CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020632

Trade Name: MERIDIA CAPSULES 5MG, 10 MG and 15 MG

Generic Name: SIBUTRAMINE HYDROCHLORIDE MONOHYDRATE

Sponsor: KNOLL PHARMACEUTICAL COMPANY

Approval Date: 11/22/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020632

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Pharmacology Review(s)	X			
Statistical Review(s)	X			
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Clinical Pharmacology Biopharmaceutics Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020632

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-632

NOV 22 1997

Knoll Pharmaceutical Company
Attention: Robert Ashworth, Ph.D.
Director, Regulatory Affairs
199 Cherry Hill Road
Parsippany, New Jersey 07054

Dear Dr. Ashworth:

Please refer to your new drug application dated August 7, 1995, received August 9, 1995, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Meridia® (sibutramine hydrochloride monohydrate) Capsules, 5, 10, and 15 mg.

We acknowledge receipt of your submissions dated August 21 and 28, September 19, November 14, and December 1, 6, 8, 13, 19, and 20, 1995; February 9, March 1, 5, 13, 14, 20, 26, and 28, April 8, 9, and 22, May 2, 12, 13, and 15, June 4, 13, and 20, July 15, 18, and 19, August 1(2), 7, 8, 12, 21, 22, 23, 27, and 30, September 20 and 23, October 4(2), 9, 15(2), 16, 17, 22, 25, and 29, November 12, 18, 25, and 26, and December 17, 1996; and January 3, 20, 23, and 29, February 5, 10,14, 27, and 28, April 15, May 23, June 4, 5, and 17, July 2, September 4, 19(2), and 29, October 8, 20, 21, 23, 28, and 30, and November 7, 13, 19, 21(fax), and 22(fax)(4), 1997. Additionally, we also refer to our November 8, 1996, approvable letter. The user fee goal date for this resubmitted application is November 23, 1997.

This new drug application provides for the use of Meridia® Capsules in the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated November 22, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician and patient (version 2) labeling submitted on November 22, 1997, and the draft bottle labels submitted on November 21, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-632. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitment specified in your submission dated November 22, 1997:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include a status summary of this commitment in your annual report to this application. The status summary should include the number of patients entered in the study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment should be clearly designated "Phase 4 Commitment."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Our laboratories have completed methods validation of the proposed NDA methodology and find that they are suitable for regulatory purposes. However, the test method for assay, determination of degradation and related substances, and dissolution include calculations that are very difficult to understand. These calculations and the explanations of terminology used in them should be simplified and/or clarified.

Please submit one market package of the drug product when it is available.

We remind you of your obligation under the Controlled Substances Act not to market the drug product until the Drug Enforcement Administration makes a final scheduling decision on it. We note that the signature of Dr. Abraham Varghese of Knoll on the form FDA 356h submitted with your original NDA signifies your commitment not to market this product until the scheduling process is complete.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Maureen Hess, M.P.H., R.D., Project Manager, at (301) 827-6411.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-632
HFD-510/Div. files
HFD-510/CSO/M.Hess
HFD-510/Colman/Haber/Steigerwalt
HFD-002/ORM (with labeling)
HFD-102/Office Director (with labeling)
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: JRhee/November 21, 1997/ a:20632.ap
Initialed by:Ripper 11-21-97/Ripper 11-22-97
final: JRhee 11-22-97 11-22-97

APPROVAL (AP) [with Phase 4 Commitment]

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-632

Knoll Pharmaceutical Company
Attention: Abraham Varghese, Ph.D.
Associate Director, Regulatory Affairs
199 Cherry Hill Road
Parsippany, New Jersey 07054

NOV - 8 1996

Dear Dr. Varghese:

Please refer to your new drug application dated August 7, 1995, received August 9, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Meridia (sibutramine hydrochloride monohydrate) Capsules, 5, 10, 15, and 20 mg.

We acknowledge receipt of your submissions dated August 21 and 28, September 19(2), November 14, and December 1, 6, 8, 13, 19, and 20, 1995, and February 9, March 1, 5, 13, 14, 19, 20, 26, and 28, April 8, 9, and 22, May 2, 10, 13, and 15, June 4, 13, and 20, July 15, 18, and 19, August 1, 7, 8, 12, 21, 22, 23, 27, and 30, September 20 and 23, and October 4(2), 9, 15, 16, 17, 22, and 25, 1996. Your May 10 submission extended the user fee due date to November 9, 1996.

Information submitted on October 9, 1996, has not been completely reviewed because it arrived late in the review cycle.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information.

A. Further analyses of blood pressure data from the clinical trials of sibutramine, especially studies 852 and 1047, are necessary to provide appropriate labeling of the drug product for monitoring blood pressure. For example, such analyses should include the distribution of the mean changes in blood pressure over the entire study period for individual patients. The relationship of early blood pressure response to later blood pressure levels also should be further analyzed. Additional details of these analyses will need to be developed in collaboration with the Division of Metabolic and Endocrine Drug Products. The outcome of these analyses may result in a request for one or more phase 4 studies to define more fully the blood pressure response to sibutramine.

B. In order that we may complete our abuse liability assessment, we request that you conduct and submit the results of the following two preclinical studies in addition to the results of your ongoing preclinical (primate self-administered) and clinical (protocols BPI 883 and BPI 893) studies.

1. Comparative Pharmacology: Comparison of the discriminative stimulus effects of sibutramine and its two active metabolites to the discriminative stimulus effects elicited by the hallucinogen MDMA.

   Results from submitted preclinical studies have suggested that the pharmacologic profiles of the metabolites BTS 54 505 and BTS 54 354 resemble that of methylenedioxymethamphetamine (MDMA). Like MDMA, these metabolites mediate their effects by both serotonin and dopamine; they all result in an increased level of dopamine and serotonin in the brain. MDMA is a potent dopamine- and serotonin-reuptake inhibitor and releasing agent. Sibutramine's active metabolites are potent dopamine- and serotonin-reuptake inhibitors, and they also possess some dopamine- and serotonin-releasing properties. Both dopamine and serotonin have been associated with mediating the addictive properties of drugs; an increase in dopamine level in the limbic system mediates the addictive properties of the psychostimulants and serotonin mediates the addictive properties of hallucinogens. MDMA produces a mixture of central stimulant and hallucinogenic effects that are mediated by dopamine and serotonin. It is believed that because of this dual mechanism, MDMA possesses both hallucinogenic- and stimulant-like discriminative stimulus properties.

   Consistent with these preclinical findings, results from the clinical trial conducted by J. Cole suggested that sibutramine may possess hallucinogenic properties. Therefore, MDMA is probably a more appropriate positive control than d-amphetamine would be. Sibutramine's active metabolites have been shown to have a neurochemical profile similar to that of MDMA. As such, they may elicit MDMA-like discriminative stimulus responses. To test this hypothesis, rats trained to discriminate between MDMA and saline should be challenged with MDMA, sibutramine, BTS 54 354, and BTS 54 505.

2. Physical-dependence-producing potential of sibutramine.

   Abstinence-associated withdrawal signs, which are the consequence of physical dependence, are a frequent motivator of continued drug intake. A study should be conducted to assess the physical-dependence potential of sibutramine in primates. We suggest a 10-week, 2-dose study in 3 male and 3 female rhesus monkeys.

For specific suggestions on the design of the protocols, we suggest you contact our Division of Anesthetic, Critical Care, and Addiction Drug Products.

C. Because several individual impurities/degradants in the drug product have been identified, individual limits should be set for each identified impurity. A limit for total unidentified impurities should also be specified. These limits should be established based on actual data for qualification batches. A justification for proposed limits should be given.

Provide revised tests and specification sheets and revised stability protocols to reflect the above.

D. Also, the following additions and revisions should be made to the labeling:

1. The following additions/modifications should be made in the DESCRIPTION section of the package insert:

   a. In the first sentence, replace the word "agent" with the word "anorectic."

   b. In the second sentence, replace the word "product" with the words "active ingredient."

   c. After the second sentence, add the sentence "It is a racemic mixture of the (+) and (-) enantiomers."

   d. In the part of the structural formula denoting the cyclobutane ring, please replace the simple square of lines with a formula in which the carbon and hydrogen atoms are indicated by the letters "C" and "H" as in other parts of the formula.

2. As conveyed to you in our facsimile transmission of March 29, we are working to standardize the content and presentation of the information in the **Pharmacokinetics** subsection of the CLINICAL PHARMACOLOGY section of the labeling. The **Pharmacokinetics** subsection should present information as appropriate under the subheadings of *Absorption, Distribution, Metabolism, and Excretion*. Following this, there should be further subheading of *Special Populations* with sub-subheadings of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Insufficiency,* and *Drug-Drug Interactions*. Where relevant information is lacking, it should be so stated.

   This subsection should also contain a table with pharmacokinetic parameters including (as appropriate) absolute bioavailability, time to peak, clearance, volume of distribution, half-life, and renal clearance for normals and each special population (including the drug's intended target population). Mean values with the coefficients of variation and 95% confidence intervals should be provided.

3. The INDICATIONS AND USAGE section should be revised to read as follows:

> Meridia is indicated for the management of obesity and should be used in conjunction with a reduced-calorie diet and exercise. Meridia is recommended for obese patients with an initial body mass index $\geq$30 kg/m^2, or $\geq$27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, and hyperlipidemia).

4. The CONTRAINDICATIONS section should be revised to read as follows:

> Meridia is contraindicated in patients
>
> - Known to be hypersensitive to sibutramine or any of its inactive ingredients.
> - Who have anorexia nervosa or bulimia nervosa
> - Taking other centrally acting appetite suppressant drugs
> - Taking monoamine oxidase inhibitors (MAOI's) (see WARNINGS)

5. The following additions/modifications should be made in the PRECAUTIONS section of the package insert:

   a. The basis for determining the multiple of the maximum human dose should be stated in the labeling. When plasma drug levels are available, human exposure should be expressed in terms of multiples of the AUC observed in preclinical studies. Until plasma levels are available, doses should be expressed in terms of multiples of mg/m^2. The calculations, based on a maximum human dose of 20 mg, should be provided but should not be included in the labeling.

   b. The sentence regarding benign tumors of testicular interstitial cells in the *Carcinogenicity* subsection should be revised as follows:

> In male rats, there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors commonly seen in rats are hormonally mediated.

In addition, the following sentence should be added: "Relevance of these tumors to humans is not known."

c. Under the *Mutagenicity* subheading, include the names of the in vitro and in vivo studies conducted.

d. The *Impairment of Fertility* statement should be moved to the **Carcinogenesis, mutagenesis, impairment of fertility** subsection. State the highest no-effect dose and relate it to human exposure on the basis of mg/m^2.

e. The **Pregnancy** subsection should revised to conform to 21 CFR 201.57(f)(6)(i)(*c*). Describe the anomalies seen in rabbits and clarify whether they were seen in the absence or presence of maternal toxicity.

f. Delete the **Labor and Delivery** subsection.

g. Revise the **Nursing Mothers** subsection to conform to 21 CFR 201.57(f)(8)(iii).

h. Delete the **Usage in Elderly** subsection.

i. Retitle the **Usage in Children** subsection **Pediatric Use** and revise it to state "Safety and effectiveness of Meridia in pediatric patients have not been established."

j. After the **Pediatric Use** subsection, add a **Geriatric Use** subsection that reads:

> Clinical studies of Meridia did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

6. The table in the ADVERSE REACTIONS section should be modified as follows:

The percentage discontinuation columns should be deleted.

The adverse events under each organ system should be listed in the order of the incidence in the Meridia patients starting with the highest incidence at the top of each list.

7. In the DOSAGE AND ADMINISTRATION section, delete the sentence "If there are no clinically significant changes in heart rate and/or blood pressure (see below) Meridia may be given in doses not to exceed 30 mg daily."

8. If the 20-mg strength and the blister packaging are to be marketed immediately, they must be added to the HOW SUPPLIED section.

9. Due to the extensive failures of dissolution at elevated temperatures, a warning to protect the capsules from heat and moisture should be included in the carton and container labels and the HOW SUPPLIED section of the labeling. the recommended storage temperature statement must be revised to conform to the USP 23 definition of either "controlled room temperature" or "room temperature."

10. Draft carton labels for all sizes of bottles and blister packs must be submitted.

11. A patient package insert must be developed.

We reserve further comment on the labeling until all the requested information is received and reviewed.

E. In addition, we request you submit a commitment to perform the following two phase 4

F. Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update this application by submitting all safety information you now have regarding this new drug. Provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Also, update this application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including (1) those involving indications not being sought in the present application, (2) other dosage forms, (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact Maureen Hess, MPH, RD, Consumer Safety Officer, telephone (301) 443-3520.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

MEDICAL REVIEW(S)

MEDICAL REVIEW

NDA #: 20-632

SPONSOR: Knoll Pharmaceuticals

DRUG: Sibutramine Hydrochloride

SUBMISSION: Two **preliminary** clinical reports: Studies SB 1049 and SB 2059

DATE OF SUBMISSION: 6/20/1996

DATE RECEIVED, M.O.: 6/27/1996

DATE OF REVIEW: 6/27/1996

8.15 SB 1049

Efficacy and Tolerability of Sibutramine versus Placebo in Maintenance or Improvement of Weight Loss, in Obese Patients, Following a Very Low Calorie Diet

OBJECTIVE/RATIONALE

8.15.1 The objective of this study was to evaluate the efficacy and tolerability of sibutramine in maintaining/improving long-term weight loss in obese patients following a very low calorie diet (VLCD).

DESIGN

8.15.2 SB 1049 was a double-blind, multicenter, parallel-group, placebo-controlled study of 160 patients conducted in France. The study comprised a 5-week run-in period, a 12-month treatment period, followed by three months follow-up. Patients were screened at week -5 and were given a four week (±1) VLCD (calorific intake was between 220 and 800 kcal/day). Those patients who achieved a weight loss of at least 6 kg were randomized into the treatment phase and received either sibutramine 10 mg once daily or matching placebo. Assessments were made at week 2, month 1 and thereafter at monthly intervals during the treatment period. Patients were followed up at months 13 and 15, i.e. for three months after cessation of therapy. Patients were stratified before starting VLCD based on BMI; one group with a BMI of > 30 and ≤ 35, and the other a BMI of > 35 kg/m^2.

PROTOCOL

POPULATION

8.15.3.1 This study included male and female patients aged with a BMI equal to or greater than 30 kg/m^2. Only those patients who lost at least 6 kg of body weight after 4 weeks on a VLCD were eligible for the study. The following exclusion criteria were used:

- Diastolic blood pressure greater than 100 mmHg.
- Obesity of endocrine origin.
- DM requiring insulin treatment.
- NIDDM not well controlled: FBS greater than 7.8 mmol/l (140 mg/dl)
- Any significant medical condition.
- Patients who have followed without success a VLCD treatment in the previous 6 months.
- Patients taking antidepressants, antiserotoninergics, barbiturates, and neuroleptics.

ENDPOINTS

8.15.3.2 Assessments included weight, waist and hip circumferences, laboratory investigations,

vital signs and adverse events.

STATISTICAL CONSIDERATIONS

8.15.3.3 All patients entering the study were included in an outcome analysis on an intent-to-treat basis. The study outcome was analyzed by analysis of variance of ranked data with factors for treatment group and centre; the treatment group-by-centre interaction was tested using the Boos-Brownie[1] approach. The point estimate of the treatment effect was calculated as the Wilcoxon-Mann-Whitney estimator P (X < Y); a 95% confidence interval was calculated by the method of Boos-Brownie with each centre given a sample dependent weighting.

Differences between the treatment groups for absolute and percentage body weight following VLCD were analyzed by repeated measures analysis of variance, with factors fitted as above plus time (week 2 and each monthly follow-up) and treatment group by time interaction. This analysis was performed on three datasets:

- All available data with no account taken of missing data (observed analysis)
- As above, but with missing values replaced by carryforward (LOCF)
- Patients who completed the active phase of the study, with a few individual missing values replaced by carryforward (LOCF completers)

The proportion of patients maintaining ≥100%, ≥50% and ≥25% of weight loss after VLCD and the proportion of patients losing ≥5% or ≥10% of screening body weight at months 6 and 12 and at endpoint was compared between treatment groups by the chi-squared test. Treatment group differences were represented by the odds ratio and associated 95% CI.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.15.4.1 Overall, 205 patients entered into the trial at 12 centres between 15 March and 27 December 1994; 45 withdrew prior to receiving any trial medication and were not included in any of the statistical tabulations. Eighty-two patients received sibutramine 10 mg and 78 received placebo; 108 patients completed the 12-month double-blind treatment phase, 60 (73%) and 48 (62%) in the sibutramine and placebo groups, respectively.

Of the 160 patients who entered the double-blind phase, only one did not provide a post-baseline assessment of body weight (in the sibutramine treatment group); therefore, 159 patients were included in the change to endpoint analysis. A total of 108 patients completed the study, but nine patients (six on sibutramine and three on placebo) were excluded from the analysis of completers as the month-12 assessment was performed more than six days after the last dosing date.

Baseline Demographic Characteristics

The treatment groups were comparable with respect to baseline demographic characteristics. The mean age of patients entering the study was 37.7 years , and the mean height was 165.0 cm . Of the 160 patients who entered the double-blind period, 154 were Caucasian (96%) and 127 were female (79%). At screening, mean body weight (i.e. before VLCD) was 104.2 kg and mean BMI was 38.3 kg/m^2

During the VLCD phase (median duration 30 days), patients lost 7.6 kg of body weight There was no difference between the two groups with respect to the amount of weight lost during the VLCD phase.

Patient Disposition

Table 8.15.4.1.1 provides the number of patients who withdrew from the study and the reason for withdrawal.

TABLE 8.15.4.1.1
Summary of patient withdrawals

Reason for withdrawal	Treatment group		
	Sibutramine 10 mg	Placebo	
Total no of patients	82	78	
Adverse event	2	5	
Lack of efficacy	1	6	
Other	19	19	
Total withdrawn	22 (27%)	30 (38%)	
Comparison of withdrawal rates	Chi-square	df	p
Overall	2.68	1	0.10
Adverse event/lack of efficacy	5.62	1	0.02

EFFICACY ENDPOINT OUTCOMES

8.15.4.2 Body Weight

There was a statistically significant change in body weight from baseline to both endpoint and month 12 for completers treated with sibutramine compared to placebo ($p<0.001$ and $p=0.004$, respectively) (Table 8.15.4.2.1).

TABLE 8.15.4.2.1
Analysis of variance for the change in mean body weight from baseline to endpoint and from baseline to month 12 for completers

Body weight (kg)	At endpoint		At month 12 for completers	
	Sibutramine 10 mg	Placebo	Sibutramine 10 mg	Placebo
Total no. of patients	81	78	54	45
Baseline	95.7	97.7	96.4	100.2
Follow-up	90.6	98.2	90.3	100.4
Change from baseline [a]	-5.2	+0.9	-5.5	+0.1
Diff between adjusted means [b]	-6.2		-5.5	
95% CI for diff	-8.2,-4.1		-8.5,-2.6	

a: adjusted for effects of centre, stratification and for the endpoint analysis treatment -by-centre interaction
b: sibutramine 10 mg minus placebo. A negative difference indicates sibutramine 10 mg favoured.

The analysis of variance of change from baseline in absolute and percentage body weight at each assessment is presented in Table 8.15.4.2.1

TABLE 8.15.4.2.1
Mean changes from baseline in absolute and percentage body weight by treatment group

Assessment	LOCF analysis		Completers	
	Sibutramine 10mg	Placebo	Sibutramine 10 mg	Placebo
No. of pts	81	78	60	48
Month 1●	-3.0 (-3.1%)	-1.5(-1.5%)	-3.1 (-3.3%)	-1.9 (-1.8%)
Month 3●	-5.8 (-6.1%)	-2.3 (-2.3%)	-6.3 (-6.6%)	-3.2 (-3.1%)
Month 6●	-6.4 (-6.6%)	-1.7 (-1.5%)	-7.1 (-7.3%)	-3.3 (-2.9%)
Month 9●	-5.5 (-5.7%)	-0.4 (-0.2%)	-6.1 (-6.3%)	-1.5 (-1.1%)
Month 12●	-5.2 (-5.3%)	+0.5 (+0.6%)	-5.6 (-5.8%)	-0.1 (+0.2%)

●p<0.05 sibutramine vs placebo; LOCF and completers datasets

These data indicate that treatment with sibutramine was associated with statistically significantly greater weight loss throughout the study.

The proportion of patients who maintained ≥100, ≥50 or ≥25% of their weight loss following VLCD was statistically significant for all time points for the sibutramine group compared to the placebo group ($p<0.01$) with the exception of ≥25% at month 6 only.

The percentage of patients who lost ≥5% or 10% of their weight loss from screening was statistically significant for all time points for the sibutramine group compared to the placebo group ($p \leq 0.001$) (Table 8.15.4.2.2).

TABLE 8.15.4.2.2
Proportion of patients losing ≥5% or ≥10% of body weight from screening

Parameter	Month 6		Month 12		Endpoint	
	Sib 10 mg	Placebo	Sib 10 mg	Placebo	Sib 10 mg	Placebo
N	73	68	55	45	81	78
≥5%	97%	82%	87%	53%	86%	55%
≥10%	71%	41%	60%	22%	54%	23%

Waist to Hip Circumference

There were no significant differences between the two groups in the change in waist to hip circumference. However, there were significant reductions in waist circumference in the sibutramine-treated subjects compared to placebo-treated patients at months 6 and 12, as well as at endpoint.

SAFETY OUTCOMES

8.15.4.3 Adverse Experiences

The most commonly reported adverse events are summarized below in Table 8.15.4.3.1.

TABLE 8.15.4.3.1
Adverse events reported by more than 5% of one or more of the treatment groups

COSTART preferred term	Number (%) of patients reporting	
	Sibutramine 10 mg n=82	Placebo n=78
ASTHENIA	9 (11%)	8 (10%)
FLU SYND	9 (11%)	8 (10%)
HEADACHE	13 (16%)	10 (13%)
INFECT	5 (6%)	3 (4%)
INJURY ACCID	7 (9%)	6 (8%)
PAIN	8 (10%)	3 (4%)
PAIN ABDO	5 (6%)	6 (8%)
PAIN BACK	11 (13%)	9 (12%)
REACT UNEVAL	2 (2%)	4 (5%)
MIGRAINE	2 (2%)	4 (5%)
VASC DIS PERIPH	1 (1%)	5 (6%)
CONSTIP	15 (18%)	4 (5%)
DIARRHEA	4 (5%)	6 (8%)
GASTROENTERITIS	4 (5%)	5 (6%)
NAUSEA	9 (11%)	3 (4%)
RECTAL DIS	6 (7%)	1 (1%)
TOOTH DIS	3 (4%)	4 (5%)
ARTHRALGIA	4 (5%)	5 (6%)
ANXIETY	9 (11%)	5 (6%)
DEPRESSION	7 (9%)	4 (5%)
DIZZINESS	2 (2%)	4 (5%)
DRY MOUTH	8 (10%)	4 (5%)
INSOMNIA	9 (11%)	7 (9%)
NERVOUSNESS	4 (5%)	1 (1%)
BRONCHITIS	12 (15%)	9 (12%)
PHARYNGITIS	17 (21%)	18 (23%)
RHINITIS	7 (9%)	5(6%)

SINUSITIS	4 (5%)	1 (1%)
RASH	2 (2%)	4 (5%)
CONJUNCTIVITIS	0 (0%)	5 (6%)
INFECT URIN TRACT	4 (5%)	2 (3%)

Those events that were more common in the sibutramine group included headache, infection, constipation, nausea, anxiety, depression, dry mouth, insomnia and nervousness. Notable adverse events reported by patients on sibutramine or placebo included palpitation in one placebo patient, tachycardia in three sibutramine patients, and hypertension and dyspnoea both reported in one patient in each group.

Vital Signs

Blood Pressure

In general, both systolic and diastolic blood pressures were higher in the sibutramine-treated subjects compared to the placebo-treated subjects; with most of the differences not reaching statistical significance. However, the change in supine diastolic blood pressure from baseline averaged over all time points for completers was significantly higher in the sibubtramine group compared to the placebo group (2.1 vs -1.4 mmHg, p=0.01; 95% CI 0.8, 6.1)). Similarly, at month 6, supine diastolic blood pressure increased by 1.4 mmHg in the sibutramine-treated subjects and decreased by 1.7 mmHg in the placebo treated patients (p=0.03; 95% CI 0.2, 6.1). It is interesting to note that all blood pressure measurements decreased in the sibutramine subjects following completion of the study (month-13 assessment). This finding highlights the pressor effect of sibutramine.

Pulse

Mean heart rate was increased in the sibutramine 10 mg group, with statistically significant differences to placebo in the following datasets: change from baseline averaged over all time points (sibutramine 6.0, placebo 3.1 bpm: p=0.02), change from baseline averaged over all time points for completers (sibutramine 6.3, placebo 0.8 bpm: p<0.001), change from baseline to month 6 (sibutramine 7.7, placebo 4.2 bpm: p=0.02), and change from baseline to month 12 (sibutramine 4.9, placebo -0.3 bpm: p=0.03). The change from month 12 to month 13 for completers was also statistically significant with a fall of -1.6 bpm for the sibutramine group and an increase of 2.8 bpm for the placebo group (p=0.04).

Clinical Laboratory Evaluations

There were statistically significant differences between sibutramine and placebo for some clinical laboratory variables; these are summarized in the Table 8.15.4.3.2

TABLE 8.15.4.3.2
Summary of statistically significant differences between sibutramine and placebo for laboratory variables

Variable	Assessment	Median as a percentage of normal range		p
		Sibutramine 10 mg	Placebo	
Triglycerides	Month 1			0.0014
	Month 6			0.02
	Endpoint			0.04
VLDL triglycerides	Month 1			0.045
	Month 6			0.04
Cholesterol	Month 6			0.055
LDL-cholesterol	Month 6			0.02
HDL-cholesterol	Month 12			0.003
	Endpoint			0.03
Total cholesterol/HDL cholesterol ratio	Month 12			0.02
LDL/HDL cholesterol ratio	Month 12			0.0099
	Endpoint			0.04
HDL+ LDL triglycerides	Month 6			0.0105
	Month 12			0.003
	Endpoint			0.008
Platelets	Month 6			0.02
Apolipoprotein A1/B ratio	Month 6			0.03
	Month 12			0.02
Apolipoprotein B	Month 6			0.049
Uric acid[a]	Month 6			0.003
	Endpoint			0.003
Chloride[a]	Month 6			0.03

a: mean as a percentage of normal range

There was no clinically relevant change in haematological parameters. Other laboratory parameters including electrolytes, urea, creatinine and liver function tests remained relatively stable and similar to placebo.

There was a mean decrease in triglycerides at endpoint compared to baseline which was statistically significant from placebo (-4.4 vs +10.0 mg/dl; p=0.04). There was also a significant mean increase in HDL on sibutramine compared to placebo (+13 vs +9 mg/dl; p=0.03), and a beneficial change in the LDL : HDL ratio (-0.4 vs -0.1; p=0.04). Although not statistically significant, cholesterol and LDL showed upward trends in both treatment groups with the largest increase in the placebo group. VLDL remained unchanged in both groups.

8.15.5 SPONSOR'S CONCLUSIONS

"Following four weeks of a VLCD, patients treated with sibutramine 10 mg for one year had an additional weight loss that was maintained and statistically significant from placebo up to and including month 12. All indices of weight loss showed consistent significant effects and there were beneficial changes in lipid profile. Sibutramine was well tolerated; the adverse event profile and changes in blood pressure and heart rate were consistent with previous studies."

MEDICAL OFFICER'S CONCLUSIONS

This 1-year study of 160 obese, primarily Caucasian female subjects, indicated that 10 mg of once-daily sibutramine is more effective than placebo in maintaining weight loss after successful completion of a 1-month VLCD. Seventy-three percent of the sibutramine-treated subjects completed the 12-month study compared to 51% of comparably treated subjects in the 12-month pivotal study SB 1047. Study enhancement — the inclusion of only those subjects who lost at least 6 kg of weight following a 1-month VLCD — may explain, in part, the favorable completion rate.

The sibutramine-treated subjects who completed the study had a mean weight loss of 5.5 kg (12 lbs), whereas the placebo subjects had a mean increase in weight of 0.1 kg (0.22 lbs). Despite an impressive reduction in body weight, the subjects treated with sibutramine for 12 months experienced an increase in supine diastolic blood pressure relative to the change in the placebo subjects (2.1 vs -1.4 mmHg; p=0.01). As observed in other sibutramine studies, pulse rate increased in sibutramine-treated subjects.

Sibutramine-induced weight loss was associated with improvements in some lipid parameters; most notably an increase in high-density lipoprotein lipid of 14 mg/dl vs 9.0 mg/dl in the placebo subjects. However, 12 months of active treatment did not significantly improve levels of total cholesterol, triglyceride, or low-density lipoprotein lipid.

8.16 SB 2059

An Evaluation of Sibutramine Compared to Placebo in the Treatment of Obese Subjects with Specific Hyperlipidemia

OBJECTIVE/RATIONALE

8.16.1 The objectives of this study were to evaluate the efficacy and tolerability of sibutramine 10 mg once daily in inducing weight loss in obese patients with hyperlipidemia and to evaluate the effect of that weight loss on the plasma lipid profile.

DESIGN

8.16.2 SB 2059 was a 16-week, multicenter, double-blind, parallel-group, placebo-controlled study conducted in Spain. Patients were restricted to a daily caloric intake of 1500 kcals. Fasted serum lipid levels were measured at screening and weeks 4, 8 and 16. Patients were followed up at week 20, i.e. one month after cessation of therapy.

PROTOCOL

POPULATION

8.16.3.1 This study included male and female subjects aged with a BMI of . Only subjects suffering from mixed hyperlipidemia defined from the guidelines of the Spanish Society of Arteriosclerosis were included in the study. These criteria were a total cholesterol (TC) in the range and/or a triglyceride level in the range of Exclusion criteria included the following:

- Diastolic BP > 95 mmHg. (patients with stabilized BP on CCB or ACE-I were allowed to participate in the study).
- Patients taking antilipid medications within 6 months of the study.
- Patients with DM or patients with a FBS > 140 mg/dl.
- Patients with any significant medical problems.
- Patients taking antidepressants, antiserotoninergics, barbiturates, or antipsychotics.

ENDPOINTS

8.16.3.2 The primary endpoint assessment included serum lipid levels which were measured at baseline and at weeks 4, 8, 16, and 20. Additional assessments included plasma insulin levels, body weight, waist and hip circumference, laboratory investigations, vital signs and adverse events. Blood pressure and pulse were measured after the patient had been seated for 5 minutes.

STATISTICAL CONSIDERATIONS

8.16.3.3 The primary measures were the changes to endpoint (last observation carried forward, LOCF) in the serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and VLDL and body weight. Comparability between the treatment groups for age, baseline body weight and baseline serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL and the LDL/HDL ratio was tested using two-sample t-tests; the serum level of triglycerides was tested using the Wilcoxon rank-sum test. The Chi-square test was used to compare the distribution of sex.

For the variables: weight loss (both absolute and percentage), total cholesterol, HDL and LDL-cholesterol, triglycerides, VLDL and the LDL/HDL ratio, the treatment groups were compared on the change from baseline/screening using repeated measures analysis of variance with factors as above but including time (weeks 2, 4, 8, 12 and 16 for weight loss and weeks 4, 8 and 16 for serum levels).

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.16.4.1 Overall, 182 patients entered into the trial, 91 randomized to sibutramine 10 mg and 91 to placebo. One hundred and sixty-six patients completed the 16-week treatment period, 81 and 85 in the sibutramine and placebo groups, respectively. Of the 182 patients who entered the double-blind phase, one sibutramine-treated patient did not provide a post-baseline assessment of body weight and two sibutramine-treated and one placebo patient did not have a value for total cholesterol.

Baseline Demographics and Lipid Levels

All patients were Caucasian with a mean age of 45.5 years mean height of 160.3 cm , mean BMI of 34.6 kg/m^2 ; and 73 % were female. The treatment groups were comparable on age, sex, body weight, BMI, and baseline (screening) measures of lipids; none of the comparisons was statistically significant. Table 8.16.4.1.1 provides the mean baseline lipid levels for the two groups.

Table 8.16.4.1.1
Baseline lipoprotein lipid levels in mg/dl

Lipid Parameter	Sibutramine n=89	Placebo n=90
TC	249	248
LDL-C	137	138
HDL-C	57	56
TG	146	159

Patient Disposition

There were no significant differences between the two groups in withdrawal rate (Table 8.16.4.1.20).

Table 8.16.4.1.2
Summary of patient withdrawals

Reason for withdrawal	Treatment group			
	Sibutramine 10 mg		Placebo	
Total no of patients	91		91	
Adverse event	2		2	
Lost to follow up	6		2	
Protocol violation	2		0	
Other	0		2	
Total withdrawn	10 (11%)		6 (7%)	
Comparison of withdrawal rates	Chi-square	df		p
Overall	1.10	1		0.30

EFFICACY ENDPOINT OUTCOMES

8.16.4.2 Lipid Levels

The rank analysis of variance for the change in triglycerides and total cholesterol from baseline to endpoint and from baseline to week 16 for completers is summarized in Table 8.16.4.2.1

Table 8.16.4.2.1
Rank analysis of variance for the change from baseline to endpoint and week 16 for completers

Variable	At endpoint		At week 16 for completers	
	Sib 10 mg	Placebo	Sib 10 mg	Placebo
Total no. of patients	89	90	78	84
Triglycerides (mg/dl)				
Baseline median	129	152	130	155
Follow up median	101	118	107	118
Median change from baseline	-23	-13	-22	-14
Difference in adjusted mean ranks	-5.21		-0.95	
Cholesterol (mg/dl)				
Baseline median	250	243	250	238
Follow up median	240	244	245	243
Median change from baseline	-9	1	-10	-2
Difference in adjusted mean ranks	-9.88		-8.30	

There were trends in favor of the sibutramine 10 mg group but no statistically significant differences between the treatment groups. In the endpoint analyses, LDL-C levels decreased in both groups (-6.0 vs -3.0 mg/dl; sibutramine vs placebo, respectively, p=0.4), and HDL-C levels did not change in the sibutramine group (0.00 mg/dl) and increased 1.0 mg/dl in the placebo group (p=0.9).

Sub-group Analysis

A sub-group analysis of those patients with values of >150 mg/dl for triglycerides at baseline showed greater falls in triglyceride levels with median changes to endpoint of -70 mg/dl for patients on sibutramine (n=31) and -37 mg/dl on placebo (n=46); p=0.05.

Body Weight

The analysis of variance for the actual change in body weight from baseline to endpoint and from baseline to week 16 for completers is presented in Table 8.16.4.2.2.

TABLE 8.16.4.2.2

Analysis of the actual change in body weight from baseline to endpoint and week 16 for completers

Body weight (kg)	At endpoint		At week 16 for completers	
	Sib 10 mg	Placebo	Sib 10 mg	Placebo
Total no. of patients	90	91	80	85
Baseline	88.3	89.9	87.5	90.0
Follow-up	80.9	84.7	79.6	84.6
Change from baseline[a]	-7.8	-5.6	-8.1	-5.7
Difference between adjusted means	-2.2		-2.4	

a: adjusted for the effect of center

The difference between the adjusted means for both datasets was statistically significantly in favor of sibutramine; p<0.001. At endpoint and at week 16, the percentage of patients with a reduction in body weight from baseline of ≥5% was 70% and 76% for patients on sibutramine compared to 49% and 51% on placebo; p=0.003 at endpoint and p<0.001 at week 16.

Waist and Hip Circumferences

Waist and hip circumferences were reduced in both treatment groups. The analysis of change to week 16 in waist circumference was, however, significantly in favor of sibutramine with a fall of 7.2 cm compared to 4.8 cm for placebo, p=0.02. Hip circumferences were reduced by 6.0 and 4.5 cm, and waist/hip ratio by 1.6 and 0.9, respectively for the sibutramine and placebo groups; the difference between the groups was in favor of sibutramine but was not statistically significant.

SAFETY OUTCOMES

8.16.4.3 Adverse Experiences

The most frequently reported adverse events (i.e. reported by more than 5% of patients) are

summarized in Table 8.16.4.3.1.

TABLE 8.16.4.3.1
Adverse events reported by more than 5% of one or more of the treatment groups

COSTART preferred term	Number (%) of patients reporting	
	Sibutramine 10 mg n=91	Placebo n=91
FLU SYND	11 (12%)	11 (12%)
HEADACHE	8 (9%)	11 (12%)
CONSTIP	16 (18%)	8 (9%)
DIZZINESS	6 (7%)	4 (4%)
ANXIETY	7 (8%)	3 (3%)
DRY MOUTH	14 (15%)	4 (4%)
INSOMNIA	7 (8%)	3 (3%)
NERVOUSNESS	5 (6%)	2 (2%)
PHARYNGITIS	11 (12%)	4 (4%)
INFECT URIN TRACT	2 (2%)	5 (6%)

Those events that were more common in the sibutramine group included constipation, dizziness, anxiety, dry mouth, insomnia, nervousness and pharyngitis.

Vital Signs

Blood Pressure

Both SBP and DBP were reduced from baseline in the sibutramine and placebo treatment groups; at week 16 for completers, the adjusted mean changes in SBP were -3.4 and -6.4 mmHg and for DBP were -1.2 and -3.6 mmHg for the sibutramine (n=80) and placebo (n=84) groups, respectively. The differences were not statistically significant.

Pulse

Heart rate (by palpation) was increased in sibutramine-treated patients compared to placebo patients at endpoint and for completers to week 16. At week 16, the adjusted mean change was +3.2 bpm on sibutramine (n=77) compared to -2.0 bpm on placebo (n=80; p=0.003).

Clinical Laboratory Evaluations

The Sponsor did not provided clinical laboratory data in this preliminary report.

8.16.5 SPONSOR'S CONCLUSIONS

"Obese patients with specific hyperlipidemia who received sibutramine 10 mg once daily for 16 weeks had statistically significant reductions in both absolute body weight and BMI compared to placebo. The changes in lipid parameters were in favor of sibutramine and statistical significance was almost achieved when patients with raised triglyceride levels at baseline were assessed in a sub-group analysis. Sibutramine was well tolerated with an adverse event profile similar to that seen in patients with uncomplicated obesity. Blood pressure was reduced from baseline overall but there was an increase in heart rate of approximately 3 bpm, consistent with that seen in previous studies."

MEDICAL OFFICER'S CONCLUSIONS

This is the first study to specifically examine the effect of sibutramine-induced weight loss on lipoprotein lipid levels in dyslipidemic patients. Much like the effects of sibutramine-induced weight loss on glycemic control in patients with NIDDM, there were no significant improvements in lipoprotein lipid levels following drug-induced weight loss.

The results of studies SB 1049 and 2059 echo the observations from other clinical studies: Sibutramine is more "effective" than placebo in producing and maintaining weight loss; however, the drug has an undesirable pressor effect and has not shown the ability to produce consistent improvements in lipid levels when compared to subjects treated with placebo.

In conclusion, the data presented in these two preliminary reports appear to lend support to this Reviewer's original recommendation of non-approval for NDA 20-632.

– 6/28/96

Eric Colman, M.D.

10-11-96

cc: NDA Arch
Hedin/Drs EColman/GTroendle/SSobel

APPEARS THIS WAY
ON ORIGINAL

JUN 25 1996

MEDICAL OFFICER'S REVIEW of the ORIGINAL SUBMISSION of NDA 20-632

DATE SUBMITTED: August 7, 1995
DATE RECEIVED, CDER: August 18, 1995
DATE RECEIVED, MEDICAL OFFICER: August 19, 1995
DATE REVIEW COMPLETED: May 10, 1996

DRUG NAME:
GENERIC NAME: Sibutramine hydrochloride monohydrate
TRADE NAME: Meridia
CHEMICAL NAME: Cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimthyl-α-(2-methyopropyl)-, hydrochloride, monohydrate, (±)

SPONSOR: Knoll Pharmaceutical Company

PHARMACOLOGICAL CATEGORY: Norepinephrine and 5-hydroxytryptamine reuptake inhibitor, appetite suppressant, anti-obesity

PROPOSED INDICATION: Treatment of obesity

DOSAGE FORM: Hard gelatin capsule containing a white to off-white

RELATED DRUGS: Effexor®, Venlafaxine (antidepressant)

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3. VOLUMES REVIEWED

1.2	1.107-1.165	1.330-1.437
1.3	1.166-1.319	1.438-1.444
1.320-1.329	1.445-1.452	1.453
1.47-1.84	1.40-1.46	2.1-2.6
1.84-1.88		

4. CHEMISTRY/MANUFACTURING CONTROLS

see chemistry review

5. ANIMAL PHARMACOLOGY/TOXICOLOGY

Sibutramine inhibits the reuptake of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) in vivo. The effects of the drug are mediated through the active metabolites: BTS 54 354 and BTS 54 505. In addition to the inhibition of reuptake of NE and 5-HT, these metabolites are weak inhibitors of dopamine (DA) reuptake. Sibutramine reduces food intake in a dose-response fashion. In animals, sibutramine increases oxygen consumption and body temperature. Studies utilizing β-blockers indicate that sibutramine indirectly stimulates β_3-receptors.

Neither sibutramine, nor its active metabolites, have any affinity for a wide range of neurotransmitter receptors. They also have no antihistaminergic, anticholinergic, or monoamine oxidase inhibitor action. Repeated doses of sibutramine down-regulate β_1, α_2, and 5-HT_{1a} receptors.

The lowest lethal oral dose of sibutramine in mice is 200 mg/kg, 100 mg/kg in rats, 40 mg/kg in dogs, and 50 mg/kg in monkeys. Sibutramine has produced no consistent effects on the hepatic or cardiovascular systems.

Sibutramine-related material binds reversibly to melanin-containing tissue in vivo. In the dog, 24 weeks of maximum tolerated doses of sibutramine produced prolonged mydriasis and inhibition of the pupillary light reflex. There were no changes detected by ophthalmoscopy or histology.

The Sponsor concludes that sibutramine is not a chemical teratogen, although studies in which the drug was administered during the end of pregnancy and during lactation indicated that there was a higher incidence of perinatal mortality associated with the drug.

Oncogenicity studies in mice at doses of 20 mg/kg showed no increase in tumor incidence. In rats, doses of sibutramine of 1, 3, and 9 mg/kg revealed a higher incidence of interstitial cell hyperplasia and adenomas in the testes; there was no increase in malignancies. The increase in adenomas of the testes was presumably related to the increased levels of LH in the treated animals. The incidence of mammary fibroadenomas was also increased in both male and

females.

Studies in mice, rats, dogs, and monkeys showed no neurotoxic effects of sibutramine. The Sponsor reports that sibutramine and its active metabolites are not mutagenic.

6. CLINICAL BACKGROUND

6.1 RELEVANT NDA - NDA 20-151 - Venlafaxine (Effexor®)

Venlafaxine was approved for the treatment of depression by the Neuropharmacology Division in 1993. Venlafaxine, like sibutramine, inhibits the reuptake of norepinephrine and 5-hydroxytryptamine.

The following adverse events were reported more commonly in venlafaxine-treated subjects compared to placebo-treated subjects:

1. Anxiety
2. Nervousness
3. Insomnia
4. Somnolence
5. Dizziness
6. Dry mouth
7. Mania/hypomania
8. Rash
9. Hypertension
10. Nausea
11. Abnormal ejaculation
12. Impotence
13. Headache
14. Asthenia
15. Sweating

There were no reported deaths associated with the use of venlafaxine at the time of the review. Limited data regarding overdose suggest that venlafaxine is not associated with respiratory depression or significant cardiovascular disturbances. Furthermore, although not systematically studied at the time of the clinical review, there was no evidence of abuse potential. A retrospective analysis of data from phase 2 and 3 studies suggest that the discontinuation of venlafaxine may be associated with a mild withdrawal syndrome.

6.2 HUMAN PHARMACOLOGY/PHARMACOKINETICS/PHARMACODYNAMICS

DOSE TOLERANCE STUDIES

BPI 801 was a double-blind, placebo-controlled study in 24 healthy males measuring the effects of 12.5 25, 50, and 75 mg of sibutramine. Doses of 50 and 75 mg produced increases in heart rate and blood pressure, QT intervals, and pupil sizes, as well as a decrease in salivary secretions. Adverse events included weakness, tremor, drowsiness, nausea, hyperactive feelings, and lightheadedness.

BPI 802 was a double-blind, placebo-controlled crossover study using amitriptyline, followed by four double-blind, ascending-dose randomization crossover treatment sessions in which subjects received a single dose of placebo or 5, 15, or 50 mg of sibutramine. The study included 12 healthy males. The 5 and 15 mg doses were categorized as antidepressants and the 50 mg dose was categorized as a CNS depressant.

BPI 803 was a double-blind, placebo-controlled study to determine the maximum tolerated sequential repeated dose of sibutramine (5, 10, 20, or 30 mg) in 32 healthy males. The 30 mg dose was not well tolerated and two subjects dropped from the study: one because of emotional sensitivity and one because of premature atrial contractions (PACs). All subjects in the 30 mg group reported complaints in the first week; these included insomnia, constipation, blurred vision, hot flashes, dizziness, anorexia, decreased libido, headache, fatigue and urinary difficulty. Inconsistent findings were noted with regard to effects on pulse and blood pressure. Mean standing pulse rate appeared to increase in the active drug groups. Some changes in ST and T wave morphology were noted at higher doses. Plasma catecholamines, notably dopamine, were elevated following 30 mg dosing.

BPI 809 was a double-blind, placebo-controlled 6-week study that examined the safety and tolerability of ascending, repeated doses of sibutramine (2.5 to 5 mg and 5 to 10 mg once daily over a six-week period, two weeks at the lower dose followed by four weeks at the higher dose) in two successive groups of normal healthy males. The study included 41 subjects. Adverse events appeared to be dose related and included tiredness, headache, and insomnia. In the 2.5-5 mg group there were chronic slight reductions in supine blood pressure (-5.8 mmHg) and increased standing systolic blood pressure (6 mmHg) at day 7. There was a dose-dependent weight loss of up to 2.9 kg.

BPI 813 was a double-blind, placebo-controlled parallel group study that assessed the safety and tolerability of ascending doses in healthy males. The subjects received 15 mg of drug daily for two weeks followed by 30 mg daily for four weeks. Change in mean supine pulse rate was 5.9 bpm at day 14 of 15 mg once daily (QD); 16.1 bpm at day 28 (two further weeks at 30 mg) and 17.2 bpm at day 42. Headache was reported by 73% of subjects, anorexia by 47%, dry mouth by 80%, and insomnia by 33%. Changes in supine and standing blood pressures were variable. Body weight decreased by 5.7% in the sibutramine-treated completers compared to a 0.9% increase in the placebo group.

MS 86004 was a double-blind, randomized, placebo-controlled, parallel-group study in 24 healthy males to evaluate the chronic effects of sibutramine on the cardiovascular system and

neurohumoral parameters. Fifteen mg twice/day for up to five days led to inhibition of uptake of noradrenaline and 5-hydroxytryptamine. The active metabolites of sibutramine (1 and 2) appeared rapidly in the plasma and reached steady state concentrations by 48 and 72 hours, respectively. The elimination half-lives were approximately 20 and 16 hours for metabolites 1 and 2, respectively. The results suggested that there is a direct relationship between metabolite concentration and inhibition of monoamine uptake. The study was terminated early because of the adverse event profile (activation of the autonomic nervous system).

PHARMACOKINETICS

Sibutramine undergoes a large first-pass metabolism which yields the active metabolites 1 and 2. Further hydroxylation of metabolite 2 and conjugation with glucuronic acid yields metabolites 5 and 6. Metabolites are excreted preferentially in urine where the major metabolites 5 and 6 are accompanied by numerous minor polar metabolites.
Based on the results of one study, the T_{max} of sibutramine is 1.2 hours, the $t_{1/2}$ is 1.1 hours and the drug has a very high oral clearance value (1750 L/Hr).

In studies of healthy volunteers, the T_{max} of the active metabolites 1 and 2 is approximately 3 hours and the elimination half-life is about 14 and 16 hours, respectively. Linear kinetics have been shown over the dose range of 10 to 30 mg with no dose-related change in elimination half-lives and a dose proportionate increase in plasma concentrations. Concentrations of metabolite 2 are twice that of metabolite 1. Steady-state concentrations of metabolites 1 and 2 are achieved within four days. The pharmacokinetics of sibutramine are the same in obese individuals as non-obese subjects.

Food delays the rate of appearance of metabolites 1 and 2 but has no effect on the extent of formation of these active metabolites. There is no evidence that gender has any effect on the pharmacokinetics of the drug. The drug metabolism is not altered in the elderly and no reduction in dose would be required according to the sponsor. Studies in patients with moderate hepatic dysfunction did not indicate any significant changes in metabolism.

The major cytochrome P450 isoenzyme responsible for sibutramine metabolism is CYP3A4. Ketoconazole does appear to inhibit metabolism of sibutramine at therapeutic concentrations.

PHARMACODYNAMICS

BPI 810 was a double-blind, placebo-controlled, parallel-group study to evaluate the cardiovascular effects of 5 and 20 mg of sibutramine in 24 males. There was a dose-related trend in overall mean heart rate increase that reached statistical significance on day 7 for the 20 mg group; the 20 mg group had a +7.6 bpm change in mean heart rate from 24-hour holter recordings during the 7-day study. The change from baseline in the total number of ventricular premature beats was 99.9 in the 20 mg group and 3.3 and -10.7 in the placebo and 5 mg groups, respectively.

PBI 822 was a placebo-controlled, fixed-dose, double-blind, crossover study that examined the cardiovascular effects of 20 mg of sibutramine in 12 healthy male subjects. The sibutramine group had significantly higher pulse rates compared to the placebo group (8.0 bpm vs -1.0 bpm).

SB 3814 was a double-blind, placebo-controlled, crossover study that examined the cardiovascular and neurohumoral effects of a single dose of 60 mg of sibutramine in the presence or absence of atenolol 50 mg vs placebo in 6 healthy males. Sibutramine alone increased blood pressure (6 mmHg relative to placebo) and heart rate (10 bpm relative to placebo. The addition of atenolol eliminated the changes on blood pressure and pulse. There were no differences between groups with respect to plasma catecholamine levels.

MS 85004 was a double-blind, 3-way crossover, placebo-controlled study that compared the cardiovascular effects of 60 mg of sibutramine with 50 mg of amitriptyline and placebo. Compared to placebo, sibutramine increased supine systolic and diastolic blood pressures, mean arterial blood pressure, and heart rate. Sibutramine had no effect on stroke volume, cardiac output, or systolic time intervals.

BPI 802 was a double-blind, single-dose, placebo-controlled crossover study with a single-blind adaptation session using amitriptyline, followed by four double-blind, ascending-dose randomized crossover treatment sessions in which subjects received placebo or 5, 15, or 50 mg QD of sibutramine in 12 healthy males. The 5 and 15 mg doses was categorized as an antidepressant and the 50 mg dose was categorized as a CNS depressant.

BPI 862 was a double-blind, placebo-controlled, parallel-group, fixed-dose study to evaluate the effects of 20 mg of daily sibutramine on the endocrine axes in 30 healthy males. The triple stimulation test with insulin, gonadorelin, and TRH diminished prolactin response on stimulation in the sibutramine group.

6.3 DIRECTIONS FOR USE

The Sponsor states that sibutramine is indicated for the long-term treatment of obesity (BMI $\geq$ 27.0 kg/m^2) and should be used in conjunction with diet and exercise. The recommended starting dose is 5 mg per day with or without food. If weight loss is inadequate **(not defined)** the dose may be titrated up every two weeks in increments of 5 mg to a total of 20 mg per day. In the absence of significant changes in heart rate and/or blood pressure **(not defined)** the drug may be given in doses not to exceed 30 mg per day.

7. DESCRIPTION OF CLINICAL DATA SOURCES

7.1.1 STUDY TYPE AND DESIGN/PATIENT ENUMERATION

Table 7.1.1.1 provides the enumeration of patients by study type and treatment group.

TABLE 7.1.1.1									
Study population	**Placebo-controlled**			**Active-controlled**		**Uncontrolled**	**All studies**		
	Sib	Pl	Comp	Sib	Comp	Sib	Sib	Pl	Comp
Uncomplicated obesity	1635	480	25	112	114	572	2319	480	139
Obese — hypertensive	72	75	0	0	0	103	126	75	0
Obese Diabetic	59	50	0	0	0	74	96	50	0
All obese	1766	605	25	112	114	749	2541	605	139
Depressed	895	349	259	0	0	313	1208	349	259
Volunteers	238	178	43	0	0	219	457	178	43
All subjects	2899	1132	327	112	114	1281	4206*	1132	441

Sib=sibutramine Pl=placebo Comp=comparator

* represents some subjects who participated in more than one study and some subjects who had prolonged periods off therapy between a double-blind study and its open extension phase and were counted as two exposures.

7.1.2 PATIENT DEMOGRAPHICS

Eighty percent of the obese participants treated with sibutramine were female. Eighty-seven percent of these subjects were between the ages The vast majority (86%) were Caucasian. The mean BMI was 33.7 kg/m^2.

Fifty-three percent of the obese patients had at least one coexisting disease at baseline. These conditions and their prevalence are shown in table 7.1.2.1

Table 7.1.2.1	
Condition	**Prevalence ((%)**
Hypertension	9
Osteoarthritis	7
Headache	4
Diabetes Mellitus	4

7.1.3 EXTENT OF EXPOSURE

As of September 30, 1994 four-hundred twenty-three subjects received sibutramine for over 52

weeks. The sponsor estimates that there were 1245 patient-years exposure to sibutramine of doses of ≥ 5 mg per day.

7.2 POST-MARKETING EXPERIENCE

Sibutramine is not marketed in the United States or elsewhere.

7.3 RELEVANT LITERATURE

The limited published literature on sibutramine does not provide any additional information to the data in the NDA.

8. CLINICAL STUDIES

PIVOTAL STUDIES

8.1 BPI 852

OBJECTIVE/RATIONALE

8.1.1 The objective of this study was to define the dose-range and efficacy of sibutramine and to assess its safety profile in patients with uncomplicated obesity.

DESIGN

8.1.2 A 24-week multicenter, double-blind, repeated-dose, placebo-controlled, parallel-group, dose-ranging weight loss study in 1047 obese patients. The following doses were evaluated relative to placebo: 1, 5, 10, 15, 20, and 30 mg per day. The primary outcome measures were the changes in body weight, vital signs and waist and hip circumferences. Consummatory behavior and safety data were also assessed. A reduction in drug dose was allowed if a subject had an intolerable adverse event.

PROTOCOL

POPULATION

8.1.3.1 This study included male and female patients aged _____ with a BMI of _____. Patients were instructed to adhere to modest caloric restriction and lifestyle and activity changes. Subjects were provided with written information on behavioral modification techniques and were instructed by a dietician to engage in a daily walking program of 20-30 minutes per day. Subjects currently treated for hypertension or diabetes mellitus (type I and II) were excluded. A scale to measure the possible withdrawal effects of sibutramine was to be included in this study; however, due to logistical difficulties it was not implemented. Subjects

with two supine or standing mean heart rates greater than 90 bpm; resting supine or standing blood pressure greater than 160 mmHg (systolic) or 95 mmHg (diastolic) were excluded. Subjects participating in a formal weight loss program within three months of the study were also excluded.

ENDPOINTS

8.1.3.2 The primary endpoints are clearly delineated and were measured in a reasonable manner. Consummatory behavior assessments were made using a hunger, satiety, appetite, craving for food type, and carbohydrate snacking scales. A three-day food intake diary was completed during the placebo run-in phase and was used by the dietitian to create a caloric restriction plan. The mean of three measurements was calculated for the vital signs. Serum levels of the drug were obtained at baseline, 12, and 24 weeks. The Hamilton depression scale was administered at baseline and at study termination at sites 03 and 06.

STATISTICAL CONSIDERATIONS

8.1.3.3 A number of efficacy variables were analyzed, some at every visit and others at weeks 12 and 24. Efficacy evaluations were conducted for continuous variables by using an ANOVA model containing factors for site, treatment, and site by treatment interaction. Comparisons of active treatments versus placebo were conducted using the Dunnett's test for continuous data and the pairwise Fisher's Exact test for categorical data. The last observation carried forward (LOCF) and observed analyses for both evaluable patients (defined as patients having at least one dose of randomized medication and at least one double-blind study visit evaluation) and completers were performed. For dose-response data only data recorded prior to a dose reduction was analyzed. For weight loss efficacy, data prior to and after a dose reduction were analyzed.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.1.4.1 A total of 1463 patients were screened. Of these, 1047 patients at seven sites were enrolled and randomized. Of these 1047 patients, 824 patients (79%) completed 12 weeks and 684 (65%) completed 24 weeks of the study. Twenty-three patients were excluded from the efficacy analyses primarily because of lack of post-baseline data. Of the population randomized, 80% were female, 78% Caucasians, 15% Black, and 7% Mexican-Americans. The mean age was 43.6 years with a range The baseline distribution of demographic variables was similar for treatment groups. The levels of compliance were comparable among the groups, and in general, were higher during the run-in and wash-out phases. There appeared to be no differences among the groups with respect to concomitant drug use initiated during the study.

Table 8.1.4.1.1 summarizes the number of patients enrolled and the numbers and reasons for discontinuation or withdrawal from the study.

TABLE 8.1.4.1.1							
1463 patients screened							
1047 patients enrolled and randomized							
1024 - 23 patients without post-baseline data not included in efficacy analyses							
Tx group	**Pl**	**1 mg**	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**
n	148	149	151	150	152	146	151
Adverse event	12	17	8	13	17	19	27
Lack of efficacy	11	11	8	2	3	4	2
Lost to foll-up	2	2	2	4	5	4	3
Prot violation	26	17	20	27	22	20	14
Other	10	7	6	5	7	3	4
Total withdrew	**61**	**54**	**44**	**51**	**54**	**50**	**50**
Completed	**87**	**95**	**107**	**99**	**98**	**96**	**101**

At week 24 there were 55% placebo; 65% 1 mg; 70% 5 mg; 63% 10 mg; 60% 15 mg; 58% 20 mg and 55% of the 30 mg subjects remaining in the study.

EFFICACY ENDPOINT OUTCOMES

8.1.4.2 Body weight

Figure 8.1.4.1.1 illustrates the mean weight loss (kg) for all dose groups combined, by month, for completers vs drop-outs. It is readily apparent that those subjects who dropped out of the study lost less weight at the time of discontinuation when compared to those subjects who completed.

Figure 8.1.4.1.1

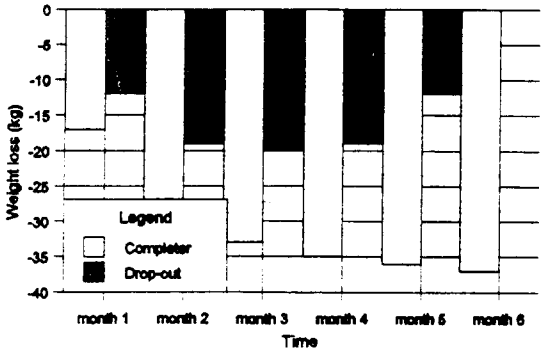


Table 8.1.4.2.1 provides the absolute change in bodyweight from baseline to week 24 for completed patients - dose reduction data retained.

TABLE 8.1.4.2.1								
Tx	**N**	**Wt loss**	**1 mg**	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**
Placebo	83	-1.3 kg	NS	*	*	*	*	*
1 mg	89	-2.4 kg		NS	*	*	*	*
5 mg	100	-3.7 kg			NS	*	*	*
10 mg	93	-5.7 kg				NS	*	*
15 mg	94	-7.0 kg					NS	NS
20 mg	89	-8.2 kg						NS
30 mg	94	-9.0 kg						

*P < 0.05 Statistical comparisons made using Tukey's HSD test.

These data indicate that there were no statistically significant differences in weight loss between the 30 mg and 20 and 15 mg groups; or between the 20 mg group and the 15 mg group, etc.

Figure 8.1.4.2.1 illustrates the percent change from baseline weight for the completers dataset - dose reduction data retained. At week 24 the percent change in body weight was statistically significantly greater for 5, 10, 15, 20, and 30 mg compared to placebo. However, only doses of 10-30 mg produced a percent weight loss that was at least 5% greater than the loss with placebo.

Figure 8.1.4.2.1

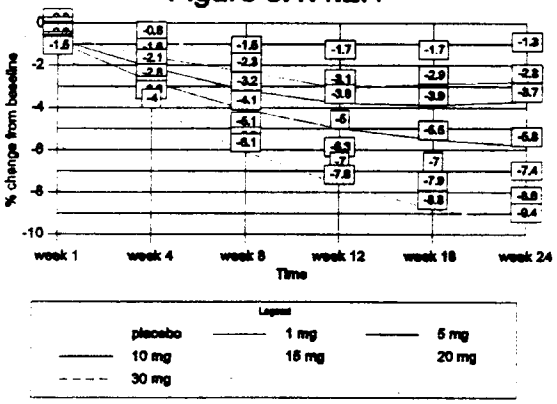


Figure 8.1.4.2.2 illustrates the percent weight loss from baseline for the intent-to-treat dataset. Although doses of 5-30 mg produced statistically significantly greater weight loss when

compared to placebo, only the 20 and 30 mg doses produced weight loss that was at least 5% greater than placebo.

Figure 8.1.4.2.2

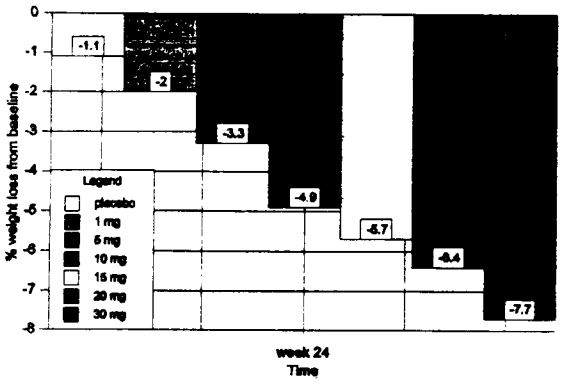


Table 8.1.4.2.2 provides the percentage of patients losing 5% of baseline body weight for the completed patients dataset.

TABLE 8.1.4.2.2

Dose-reduction data retained				Completed patients, n=683			
Wk	**Placebo**	**1 mg**	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**
12	18%	25%	40%*	52%*	64%*	69%*	76%*
24	20%	25%	37%*	60%*	67%*	72%*	77%*

*P<0.001 compared to placebo

Table 8.1.4.2.3 provides the percentage of patients losing 5% of baseline body weight for the strict intent-to-treat dataset (all subjects randomized are included).

TABLE 8.1.4.2.3

Dose-reduction data retained				Intent-to-Treat Analysis n=1047			
Wk	**Placebo**	**1 mg**	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**
12	11%	16%	33%*	37%*	45%*	49%*	57%*
24	11%	15%	27%*	38%*	41%*	45%*	48%*

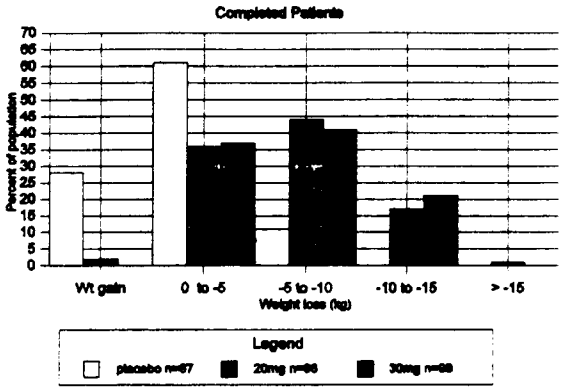
*P < 0.001 compared to placebo

Although far fewer subjects achieved 5% or greater weight loss in the intent-to-treat analysis, the results are similar, statistically, between the intent-to-treat and the completers analyses.

However, there were no statistically significant differences in the proportion of subjects losing at least 5% of initial body weight between 30 mg and 20 mg, 20 mg and 15 mg, 15 mg and 10 mg, etc.

Figure 8.1.4.2.3 illustrates the frequency distribution of weight loss in kg for the placebo, 20 mg, and 30 mg groups at week 24.

Figure 8.1.4.2.3



These data suggest that the 20 and 30 mg doses are essentially equivalent.

Dose-response data

Regression analyses from the various datasets indicate that the slope of the line relating weight loss to log-drug dose is steepest between 5-20 mg. Again, these data support the contention that efficacy is not appreciably increased with doses above 20 mg per day.

Correlation between drug dose and plasma concentration of active metabolites

There were statistically significant correlations between drug dose and plasma concentrations of the active metabolites ($r=0.59$, $p=0.0001$ and $r=0.76$, $p=0.0001$ for metabolite 1 at week 12 and 24, respectively; and $r=0.57$, $p=0.0001$ and $r=0.69$, $p=0.0001$ for metabolite 2 at week 12 and 24, respectively). These data are from 470 patients at week 12 and 398 subjects at week 24.

There were statistically significant correlations between the change in body weight at week 12 and 24 with the plasma concentrations of metabolites 1 and 2 as shown in table 8.1.4.2.4.

TABLE 8.1.4.2.4				
	Correlation with metabolite 1		**Correlation with metabolite 2**	
	Week 12	Week 24	Week 12	Week 24

TABLE 8.1.4.2.4								
	Correlation with met: bolite 1				Correlation with metabolite 2			
	r	p	r	p	r	p	r	p
Δ Wt loss	-0.19	0.0001	-0.23	0.0001	-0.34	0.0001	-0.39	0.0001

Waist and Hip Circumferences

Statistically significant decreases in waist circumference were observed with doses of 10-30 mg QD at week 24. The changes in hip circumferences were similar to those of the waist circumferences and thus there were no changes in the waist to hip ratios. Waist circumference represents a crude index of visceral fat and the correlation between changes in waist circumference and visceral fat is modest and varies by gender and age. Thus, valid conclusions regarding changes in visceral fat content cannot, in general, be made based on changes in waist circumference. These relationships are weakened further because of the multicenter design and interobserver variations in waist circumference measurements. CT scanning represents the most accurate method of measuring changes in visceral fat content. The Sponsor should be encouraged to conduct such studies.

Consummatory Behavior Measurements

Changes in the overall appetite and carbohydrate craving scales followed a pattern in which there was a dose-dependent decrease in the variable up to weeks 4-6. Thereafter, appetite and carbohydrate craving increased slightly, but still remained below baseline values at week 24.

SAFETY OUTCOMES

8.1.4.3 Adverse experiences

For treatment-emergent events, two datasets were used: (1) the randomized dataset comprised those data collected at the randomized dose. If a patient had a dose reduction, adverse event data reported at the lower dose were not included in this dataset; (2) The actual dataset included those data collected at the randomized dose and after a dose reduction. Therefore, in this dataset, all adverse event information is summarized. In preparing this dataset, two conventions were used: for incidence tables an event occurring at two dose levels was assigned to the lower dose and for both incidence and occurrence tables the treatment group numbers reflect the number of patients randomized to that dose plus the number of patients who fell back to that dose.

It should be noted that there were some events reported in the "actual dataset" that were statistically significantly different between active treatment and placebo (increased appetite, hyperkinesia, nervousness, ejaculatory abnormality, and epididymitis) that were not statistically

significantly different among the groups in the "randomized dataset". Similarly, there were two events (asthenia and ecchymosis) that did not occur at a statistically significantly different rate in the "actual dataset" but did in the "randomized dataset."

The number and percent of patients exposed by duration of double-blind therapy is presented in table 8.1.4.3.1.

TABLE 8.1.4.3.1

Tx group	Duration of double-blind therapy (weeks)								
	≤1	>1≤4	>4≤8	>8≤12	>12≤16	>16≤24	>24≤28	>28≤32	>32≤36
Placebo n=148	99%	80.4%	78.4%	71.6%	65.5%	61.5%	60.1%	31.8%	2.0%
1 mg n=149	100%	86.6%	85.2%	79.2%	76.5%	72.5%	67.8%	32.2%	2.7%
5 mg n=151	100%	84.8%	82.8%	80.8%	76.8%	74.8%	41.1%	2.0%	0.0%
10 mg n=150	99%	81.3%	80.7%	77.3%	74.0%	70.7%	69.3%	39.3%	2.0%
15 mg n=152	100%	85.5%	84.2%	78.3%	74.3%	69.1%	68.4%	35.5%	3.3%
20 mg n=146	100%	84.9%	84.2%	78.1%	74.7%	74.0%	71.9%	35.6%	2.1%
30 mg n=151	100%	92.1%	89.4%	84.1%	80.1%	76.2%	70.9%	37.1%	0.0%
total n=1047	100%	85.1%	83.6%	78.5%	74.6%	71.3%	64.2%	30.5%	1.7%

The duration of exposure appeared to be equal in the various dosage groups.

A number of patients had their dose reduced during the study. Table 8.1.4.3.2 illustrates the percent of patients whose dose was reduced during the double-blind phase presented by reason and initial dose.

TABLE 8.1.4.3.2

Reason	Placebo	1 mg	5 mg	10 mg	15 mg	20 mg	30 mg	Total
Did not reduce dose	94%	93%	91%	88%	87%	77%	71%	86%
Reduced dose	6%	7%	9%	12%	13%	23%	29%	14%
Adverse event	2%	5%	3%	7%	4%	10%	15%	6%
Blood pressure○	3%	1%	1%	3%	4%	3%	9%	3%

TABLE 8.1.4.3.2								
Reason	**Placebo**	**1 mg**	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**	**Total**
Pulse rate●	1%	1%	1%	0%	3%	8%	3%	2%
Other	0%	1%	4%	2%	3%	1%	2%	2%
Unknown	0%	0%	1%	1%	0%	1%	1%	0%

○ dose was reduced for patients whose mean systolic blood pressure was > 160 mmHg or whose mean diastolic blood pressure was > 95 mmHg.

● dose was reduced for patients whose mean pulse rate was > 100 bpm.

These data suggest that the 20 and 30 mg doses were not as well tolerated compared to the lower doses. In particular, the 30 mg dose group had a larger percentage of subjects who had their dose reduced because of an increase in blood pressure.

Based on the criteria of an incidence of greater than 1% in a sibutramine group and an incidence greater than placebo, the following adverse events were associated with permanent dose reductions due to sibutramine treatment: asthenia, headache, chest pain, hypertension, palpitations, tachycardia, anorexia, nausea, agitation, anxiety, dizziness, dry mouth, hyperkinesia, insomnia, nervousness, tremor, rash, and dyspnea. Events that occurred with a statistically significantly (or near statistically significantly) greater incidence in the sibutramine group included anorexia ($p=0.005$), agitation ($p=0.066$), dry mouth ($p<0.001$), insomnia ($p<0.001$), tremor ($p=0.068$), rash ($p=0.07$), and dyspnea ($p=0.061$).

The percentages of patients with at least one **treatment-emergent severe adverse** event were as follows: placebo (8%), 1 mg (13%), 5 mg (14%), 10 mg (14%), 15 mg (15%), 20 mg (13%), and 30 mg (15%).

When the adverse event rates for all the drug treatment groups were combined and compared to the rate in the placebo group the following adverse events were statistically more common in the active treatment groups compared to the placebo group:

1. Vasodilatation (2.8 vs 0.0%, $p=0.038$)
2. Anorexia (25 vs 13%, $p<0.001$)
3. Constipation (11 vs 4%, $p=0.009$)
4. Dry mouth (22 vs 6%, $p<0.001$)
5. Insomnia (13 vs 7%, $p=0.039$)

Table 8.1.4.3.3 illustrates the percentage of patients, by dosage, reporting at least one adverse event that was statistically significant compared to placebo.

TABLE 8.1.4.3.3								
	Placebo	**1mg**	**5mg**	**10mg**	**15mg**	**20mg**	**30mg**	**P Value**
Hypotesnion	0	0	0	0	0	2	0	0.017

TABLE 8.1.4.3.3								
	Placebo	1mg	5mg	10mg	15mg	20mg	30mg	P Value
Palpitation	1	2		5	3	4	6	0.004
Tachycardia	1	1	2	4	8	7	3	0.001
Vasodilitat	0	1	2	2	2	5	5	0.015
Anorexia	12	20	19	19	21	32	32	0.001
Inc appetite	8	11	17	17	14	12	21	0.017
Constipation	4	7	13	11	12	12	8	0.031
Diarrhea	5	10	6	4	2	3	3	0.011
Dyspepsia	7	4	4	4	8	5	13	0.017
Nausea	4	3	4	3	5	8	13	0.002
Dry mouth	6	6	12	17	26	32	32	0.001
Hyperkinesia	0	0	1	0	0	3	1	0.030
Insomnia	6	12	8	9	10	10	25	0.001
Nervousness	6	5	5	6	8	12	11	0.044
Dyspepsia	0	1	1	1	1	1	5	0.024
Sweating	0	0	1	1	3	4	3	0.026

p value is from a Cochran-Mantel-Haenszel Chi-square test
The majority (85%) of adverse events were considered mild in severity.

Ordered from highest to lowest difference between placebo and active treatment, these adverse events were: dry mouth, anorexia, appetite increase, nausea, tachycardia, nervousness, dyspepsia, palpitations, vasodilatation, dyspnea, and sweating.

Based on the criteria of an incidence greater than 1% in two treatment groups and an incidence greater than placebo, the events listed in table 8.1.4.3.4 appeared to be associated with **treatment-related discontinuation.**

TABLE 8.1.4.3.4							
Event	**placebo** n=148	**1 mg** n=149	**5 mg** n=151	**10 mg** n=150	**15 mg** n=152	**20 mg** n=146	**30 mg** n=151
Hypertension	1	0	1	0	2	3	7
Palpitations	0	0	0	2	0	0	2
Tachycardia	1	0	0	0	2	4	1
Insomnia	1	1	0	1	0	3	2
Dyspnea	0	2	0	1	2	0	1

Discontinuations from the study due to hypertension were more numerous for sibutramine doses 15-30 mg relative to placebo.

Table 8.1.4.3.5 provides the details of the **serious adverse events** reported during the study.

TABLE 8.1.4.3.5

number	sex	age	dose	drug duration	event	comment
2010	M	38	1mg	8wk	near syncope	withdrew at 10wk, no f/u
5053	F	38	1mg	8wk	gastric distress	withdrew 12 wks, cholecystectomy
1122	F	45	5mg	17wk	hemorrhage L eye	completed study
4023	M	20	5mg	2-days post	severe depression	recovered after 6-days
2153	M	59	10mg	8wk	syncope	recovered, completed
2069	F	38	15mg-10mg	7wk	cva after 2wk of 10mg	sxs resolved 1 day. No f/u
6145	F	36	15mg	5days	anxiety	patient withdrew
1048	F	48	20mg	3wk	L eye flashes	completed at 10 mg
1139	F	39	20mg-10mg	13days	seizure-like activity	patient withdrawn at 13 days
1141	F	46	20mg	1 day	moderate depression	patient withdrew and recovered
2006	F	60	20mg-10mg	2wk	moderate tachycardia	patient withdrawn
1107	M	61	30mg	4 days	anxiety	patient withdrew, anxiety resolved
2169	F	25	30mg-15mg	7wk	anxiety,tachycardia,suicide attempt	patient withdrawn for counseling
5118	F	44	30mg	9days	breast lump and toxic thyroid	lump resolved after thyroidectomy
7019	F	53	30mg	24wk	thyroid nodule	lobectomy
1016	M	53	15mg	2wk	hypertension	started on vasotec and completed study. Had a hx of untreated hypertension.

It is of interest to note that no serious adverse events were reported for subjects receiving placebo.

Dysmenorrhea was reported by 3% of women in the 10 mg group (p=0.032 vs placebo) during the placebo washout period. There were three serious post-treatment adverse events reported. One subject in the placebo group was diagnosed with squamous cell carcinoma of the throat; another patient who received 20-10 mg of sibutramine developed nervousness and tachycardia after 8 wk of therapy and was withdrawn from the study at 18 weeks because of hypertension (150/102), he then developed chest pain at 6 weeks post-study, he ruled out for a myocardial infarction; the third patient was randomized to 30 mg of drug treatment which was reduced to 15

mg for constipation and she completed the study. During the post-treatment period she was diagnosed with vaginal dysplasia.

Correlation between the change in bodyweight with the number of unique adverse events

It is interesting to note that there were statistically significant correlations between the change in body weight with the number of unique adverse events in the 10, 15, 20 ,and 30 mg groups, but not in the 5 mg, 1 mg, or placebo groups.

Clinical laboratory evaluations

There was a dose-related increase in the mean platelet count for the doses 10-30 mg; however, there were no clinically significant changes. There were isolated abnormalities in serum chemistry values, but none were clinically significant (i.e. $\geq$ 3 times upper limit of normal for AST). One female developed an elevated ALT value that had not resolved by her last evaluation and two subjects developed hyperglycemia that was present at their last evaluation. There were no significant patterns of change in the thyroid function tests during the study.

Lipoprotein lipids

Although the lipid levels tended to change in a favorable directions with sibutramine, there were no obvious dose-response relationships and no consistent, statistically significant changes between the active-treated groups compared to the placebo group. The Sponsor indicated that compliance with fasting prior to the sampling was variable.

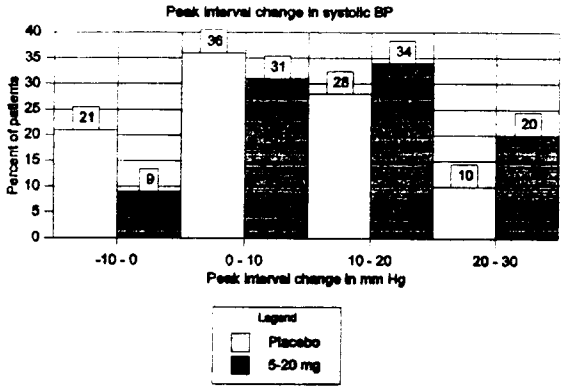
Vital signs

Systolic BP

Mean increases in supine systolic blood pressure were observed at all time points for sibutramine patients relative to placebo. However, a dose-response relationship was not obvious. For all sibutramine doses, changes in systolic pressure tended to rise and plateau at week 8. Mean ranges during the double-blind treatment period for the placebo group were -1.3 to 1.7 mmHg, and for the sibutramine groups were -0.1 to 7.5 mmHg. Statistically significant overall treatment effects were noted at weeks 6, 8, 10, 12, 15, 18, and 21.

Figure 8.1.4.3.1 illustrates the peak interval change in 5 minute supine systolic blood pressure for doses of 5-20 mg combined vs placebo.

Figure 8.1.4.3.1



These data illustrate that a greater percentage of placebo patients had a peak interval change of -10-0 mmHg compared to sibutramine-treated patients and a greater percentage of sibutramine subjects had a peak interval change of 20-30 mmHg relative to placebo subjects.

APPEARS THIS WAY
ON ORIGINAL

Diastolic BP

Changes in supine diastolic blood pressure tended to mimic those of supine systolic blood pressure. Increases in diastolic pressure for sibutramine doses relative to placebo were noted, although an obvious dose-response relationship was not apparent. Similar to changes in systolic blood pressure, diastolic blood pressures tended to rise and plateau at week 8. There was no evidence that the pressures declined over the course of the 24-week study. Changes for placebo ranged from -1.3 to 1.3 mmHg, and for sibutramine doses the range was -0.7 to 5.0 mmHg. Statistically significant overall treatment effects were noted at weeks 4, 6, 8, 10, 12, 15, 18 and 21, as well at weeks 27 and 30 (3 and 6-weeks post-treatment). The only consistent, statistically significant findings relative to placebo were for the 20 mg dose group at weeks 6, 8, 10, 12, 15, 18, and 24. Three patients had significant increases from baseline for supine diastolic blood pressure: (1) patient #3006, taking 20 mg daily had an increase from 82 to 118 mmHg, (2) patient #3027, taking 30 mg daily had an increase from 86 to 110 mmHg and, (3) patient #7059, also taking 30 mg daily had an increase from 82 to 108 mmHg.

Figure 8.1.4.3.2

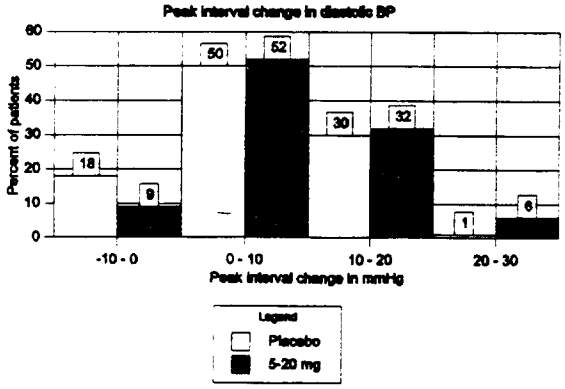


Figure 8.1.4.3.2 illustrates the peak interval change in 5 minute supine diastolic blood pressure for doses of 5-20 mg combined vs placebo.

APPEARS THIS WAY
ON ORIGINAL

Similar to the peak interval changes in systolic blood pressure, a greater percentage of placebo patients had a peak interval change in diastolic blood pressure of -10-0 mmHg compared to sibutramine patients, whereas, a greater percentage of sibutramine patients had a peak interval change of 20-30 mmHg compared to placebo subjects.

Regarding changes in standing diastolic pressure, one placebo patient and 12 sibutramine-treated patients had clinically significant increases from baseline in standing diastolic pressure. The values in mmHg are noted below.

Treatment	Baseline value	Abnormal value
Placebo	92	108
5 mg	82	110
	74	110
	78	110
10 mg	82	108
	78	107
	94	110
20 mg	74	106
30 mg.	70	110
	90	110
	80	110
	80	108
	60	108

APPEARS THIS WAY
ON ORIGINAL

Pulse

Consistent increases in mean supine pulse rate relative to placebo were observed for the 5-30 mg doses. Increases tended to be dose-related. The changes reached a maximum by week 8 and plateaued thereafter. Changes for placebo through week 24 ranged from -0.6 to 2.8 bpm, and for sibutramine from 0.0 to 8.8 bpm.

Table 8.1.4.3.6 summarizes the mean changes (±SD) in vital signs from baseline to weeks 12 and 24.

TABLE 8.1.4.3.6								
Parameter	**Week**	**Placebo**	**1 mg**	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**
	12 (n)	99	114	125	115	108	111	117
	24 (n)	84	92	103	95	94	89	96

TABLE 8.1.4.3.6								
Parameter	**Week**	**Placebo**	**1 mg**	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**
Supine❶ SBP	12	0.6 (12)	2.0 (10)	3.3 (11)	5.1 (10)•	3.7 (11)	5.2 (12)•	3.5 (13)
	24	1.7 (12)	1.2 (11)	2.5 (11)	4.2 (11)	3.4 (12)	5.0 (12)	4.1 (12)
Standing SBP	12	-0.7 (11)	1.0 (10)	1.9 (12)	4.0 (12)•	2.8 (13)	4.2 (12)•	1.6 (14)
	24	0.5 (13)	0.8 (12)	0.8 (12)	4.1 (12)	4.5 (12)	3.5 (13)	3.3 (14)
Supine DBP	12	0.7 (8)	0.3 (7)	2.4 (9)	2.9 (8)	2.8 (8)	4.9 (10)•	2.1 (8)
	24	0.8 (8)	0.3 (7)	2.1 (8)	2.8 (8)	2.7 (8)	4.0 (9)•	3.3 (8)
Standing DBP	12	0.6 (8)	-1.1 (7)	1.4 (8)	2.0 (9)	4.1 (8)•	3.3 (10)	1.6 (9)
	24	0.5 (9)	-1.6 (9)	0.2 (10)	2.4 (9)	4.1 (8)•	2.6 (8)	2.3 (9)
Supine❶ pulse	12	0.6 (7)	0.3 (7)	3.6 (7)•	4.4 (7)•	6.3 (9)•	7.0 (8)•	6.6 (9)•
	24	0.6 (6)	0.3 (8)	3.3 (8)	6.0 (8)•	6.1 (8)•	7.0 (9)•	5.3 (8)•
Standing pulse	12	0.2 (8)	0.8 (8)	3.6 (8)•	4.0 (9)•	6.6 (9)•	7.9 (9)•	7.3 (10)•
	24	-0.3 (7)	-0.6 (8)	2.8 (9)	4.4 (8)•	5.8 (8)•	7.8 (10)•	5.3 (9)•

❶Blood pressure in mm Hg; pulse in bpm.
• $p<0.05$ active treatment vs placebo

Interestingly, there were statistically significant correlations between the plasma concentrations of metabolites 1 and 2 with the changes in pulse rate at week 12, but not with the changes in blood pressure.

Electrocardiograms

There were dose-related increases in heart rate. The changes in heart rate reached a maximum by week 2 and remained constant thereafter. The changes in heart rate at week 24 were as follows: placebo, 1bpm; 1 mg, 3 bpm; 5 mg, 5 bpm; 10 mg, 5 bpm; 15 mg, 5 bpm; 20 mg, 6 bpm; 30 mg, 10 bpm. At each visit, (except week 24, 10 mg) the sibutramine 10, 15, 20, and 30 mg groups had statistically significant increases in heart rate compared to placebo. Significance for the sibutramine 5 mg group was only occasional. At week 6 and thereafter, the PR intervals for the sibutramine groups were shortened when compared to the changes in the placebo group. These differences were not clinically significant. There were no clinically meaningful changes in the QRS or QT intervals in the sibutramine groups relative to the changes in the placebo group. There were several patients who had an increase in the number of premature atrial contractions (PACs) during the study; however, all but one of these subjects had a reduced number of PACs by week 24. There were a number of patients who had an increase in the number of premature ventricular contractions (PVCs) from baseline during the study. Five sibutramine subjects went from 0 PVCs/2min at baseline to greater than 5 PVCs/2min during the study. Three placebo

patients developed PVCs during the study. Most of the patients had persistent PVCs at the final evaluation. The clinical significance of a potential increase in the rate of PVCs in unknown, but does raise some concern if the drug is used by patients with known or occult coronary heart disease.

Neuropsychiatric evaluations

There were no statistically or clinically significant changes in the scores on the Hamilton Depression Scale for sibutramine or placebo subjects. Changes in the Modified Norris Assessment were, in general, not statistically significant. The absolute changes favored the sibutramine group for the categories of mental and physical sedation, tranquilization, and other feelings. No data were obtained regarding withdrawal effects.

8.1.5 SPONSOR'S CONCLUSIONS

"The results of this study indicate that in the healthy, obese patients treated in this study sibutramine, in doses of 5-30 mg, was both safe and effective."

8.1.6. MEDICAL OFFICER'S SUMMARY AND CONCLUSIONS

This Reviewer agrees with the Sponsor's conclusion that doses of 5-30 mg were "effective." The 5% responder analysis in both the completers and intent-to-treat datasets verified that doses of 5-30 mg were more effective in achieving a 5% weight loss when compared to placebo.

The adverse events that appeared to be drug related were, in general, not serious and reflected the pharmacological actions of the drug: increased serotonergic and adrenergic activity. Of concern, however, was the dose-related increase in pulse rate and a trend for an increase in blood pressure in the patients treated with doses greater than 5 mg QD. Nearly 30% of the subjects randomized to 30 mg had their dose reduced; fifteen percent because of an adverse event and 9% because of increase in blood pressure (SBP > 160 mmHg or DBP > 95 mmHg). Seven subjects in the 30 mg group were withdrawn from the study because of a hypertensive response compared to one subject in the placebo group. The inverse association between sibutramine-induced weight loss and blood pressure is a critical, negative feature of the drug, and will play a major role in the risk — benefit analysis.

Given the increased incidence of adverse events and hypertension in the 30 mg group, coupled with the dose-response curve plateauing at 20 mg and the lack of statistically significant differences in weight loss between the 20 and 30 mg doses, this Reviewer believes that the elimination of the 30 mg dose would increase safety without reducing overall efficacy.

8.2 BPI 852X

OBJECTIVE/RATIONALE

8.2.1 The objective of this study is to assess the long-term safety, tolerability and efficacy of sibutramine for up to 24 months.

DESIGN

8.2.2 A multicenter, open-label, flexible-dose study to evaluate the long-term effects of sibutramine administered for up to 24 additional months to relatively healthy obese patients who have previously participated in BPI 852.

PROTOCOL

POPULATION

8.2.3.1 Male and female patients between the ages of _____ years with a BMI of _____ The following patients were not eligible for this study: patients who discontinued from BPI 852 prior to week 24, or who discontinued at week 24 due to an adverse event, and those who were noncompliant with dosing in BPI 852.

ENDPOINTS

8.2.3.2 The primary endpoints are the assessment of long-term safety and tolerability of sibutramine. Secondary endpoints included the assessment of optimal doses of sibutramine in inducing and maintaining weight loss for up to 24 months, and assessing withdrawal potential during a 6-month follow-up period.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.2.4.1 Six-hundred eighty-three patients completed 24 weeks of study BPI 852. Five-hundred ninety-one of these patients were screened for BPI 852X, and five-hundred seventy-two patients received active treatment. Two-hundred thirty-five patients had withdrawn from the study as of September 30, 1994; 72 due to adverse events, 24 due to lack of efficacy, 24 were lost to follow-up, 82 discontinued due to protocol violations, and 33 discontinued for other reasons.

SAFETY OUTCOMES

8.2.4.2 There have been no deaths reported in this study. Of the 72 patients who were withdrawn from the study because of an adverse event a large percentage were due to hypertension, depression or mood alterations, and headaches. Refer to the overview of safety section for details on safety data submitted 12/19/95.

8.3 SB 1047 UK

OBJECTIVE/RATIONALE

8.3.1 The aim of this study was to evaluate the long-term (1 year) efficacy, tolerability, and safety of sibutramine in patients with uncomplicated obesity.

DESIGN

8.3.2 This was a 12-month, multicenter, double-blind, placebo-controlled, parallel-group study of 10 and 15 mg QD of sibutramine in 485 patients. There was a 1-month follow-up period after the 12-month active treatment phase. The principle outcome variable was the change in body weight. Additional parameters that were measured include vital signs, waist and hip circumferences, and patient self assessments of hunger, satiety, and appetite.

PROTOCOL

POPULATION

8.3.3.1 The patient population consisted of 485 subjects of which 20% were men and 80% women. The mean age was 42 years with a range of_____ years. The vast majority (> 98%) were Caucasian. The average BMI was 32.7 kg/m^2 with a range of Patients treated for hypertension were allowed to participate in the study if their condition had been stabilized by medication(s) for six months or more.

ENDPOINTS

8.3.3.2 The primary efficacy endpoint was change in body weight. This parameter was measured during the 2 week placebo run-in period and monthly thereafter. All participating study centers were provided with the same scale to measure body weight. Compliance, adverse events, and concomitant medication use were evaluated at each monthly visit. Laboratory investigations and ECGs were conducted at baseline, and months 6 and 12. Total cholesterol, triglyceride, and glucose levels were measured in the **non**fasting state. Blood pressure and pulse measurements were conducted with the subjects in the seated position.

STATISTICAL CONSIDERATIONS

8.3.3.3 All statistical tests were 2-tailed with $p<0.05$ considered significant. All analyses were performed on an intent-to-treat basis. Patients who completed the study were assigned to one of 10 categories based on the percentage of weight loss over the course of the study: withdrawal because of treatment success; loss of >20% of initial bodyweight; 15.1%-20.0% lost; 10.1%-15.0% lost; 5.1%-10.0% lost; 0.1%-5.0% lost; no change; weight gain; withdrawal because of adverse event; and withdrawal because of lack of efficacy. This analysis was repeated on the dataset formed after patients who withdrew for reasons unconnected with the safety and efficacy of the drug were excluded. The differences between the treatment groups in weight loss were

analyzed using repeated measures analysis of variance. The repeated measures analyses were performed on four datasets: 1) all available data with no account taken of missing values; 2) all available data but with missing values estimated by LOCF; 3) patients who completed the 12-month double-blind phase of the study; and 4) all available data with the addition that, for the within-group tests, the missing values were replaced by predicted values calculated from the model fitted to the data. Patients who did not have an assessment of body weight following the 1-month assessment were not included in the analyses for datasets 1 and 4.

RESULTS

POPULATION ENROLLED/ANALYZED

8.3.4.1 Five-hundred and ten patients were enrolled in the study. Twenty-five withdrew during the washout period, thus 485 patients entered the double-blind phase. A total of 256 completed the 12-month study. Eighty of 163 completed the study in the placebo group, 82 of 161 completed in the 10 mg group, and 94 of 161 completed in the 15 mg group.

The groups were comparable at baseline with respect to mean age and mean BMI. However, the male subjects in the 10 mg group weighed less than the male subjects in the other two groups. The mean BMI values were similar for the male patients in all groups.

Ten subjects in the placebo group, 7 in the 10 mg group, and 5 in the 15 mg group started antidepressive, tranquillizers, or psychomimetics during the study. Eleven subjects in the placebo group, 7 in the 10 mg group, and 8 in the 15 mg group started antihistamine/anti-allergic medications during the study. Fifteen subjects in the placebo group, 10 in the 10 mg group, and 14 in the 15 mg group started corticosteroid therapy during the study. Thirty-eight placebo subjects: 55 in the 10 mg group and 59 in the 15 mg group started antibiotic or other antibacterial therapy during the study

Table 8.3.4.1.1 summarizes the enrollment and withdrawals from the study

TABLE 8.3.4.1.1			
510 ENROLLED			
25			Withdrew during washout period
485			Randomized
Placebo n=163	10 mg n=161	15 mg n=161	Treatment groups
48	56	44	Withdrew-other reasons
34	23	22	Withdrew-lack of efficacy and/or adverse event

Placebo n=163	10 mg n=161	15 mg n=161	Treatment groups
81	82	95	completed 12-months
4	2	1	excluded from completers analysis

Fifty percent, 51%, and 59% of the placebo, 10 mg, and 15 mg subjects, respectively completed the study.

EFFICACY ENDPOINT OUTCOMES

Body weight

Table 8.3.4.2.1 illustrates the results of the categorical analysis of weight loss for all patients.

TABLE 8.3.4.2.1

Outcome category	Frequency		
	Placebo n=163	**10 mg n=161**	**15 mg n=161**
Treatment successes	1	0	1
> 20% weight loss	1	3	6
15.1%-20.0% weight loss	1	11	8
10.1%-15.0% weight loss	4	11	23
5.1%-10.0% weight loss	16	21	24
0.1%-5.0% weight loss	29	21	18
No change	1	0	2
Weight gain	28	15	13
Withdrew-other reasons	48	56	44
Withdrew-lack of efficacy and/or adverse event	34	23	22

The sibutramine 10 and 15 mg groups had more favorable outcomes compared to the placebo group ($p<0.05$ and $p<0.001$, respectively). The two drug treatment groups did not differ statistically from one another.

Table 8.3.4.2.2 illustrates the adjusted (*) mean weight loss (kg) for each of the 12 months of the study for completers.

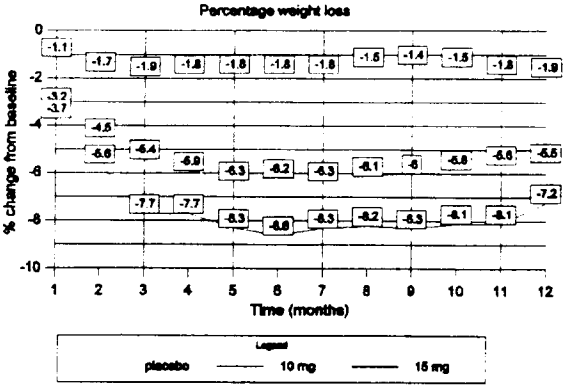
TABLE 8.3.4.2.2			
Month of study	**Placebo** n=76/163	**10 mg** n=80/161	**15 mg** n=93/161
1	-1.0[a]	-2.8[b]	-3.2[b]
2	-1.5[a]	-4.0[b]	-4.8[c]
3	-1.8[a]	-4.7[b]	-6.0[c]
4	-1.6[a]	-5.1[b]	-6.6[c]
5	-2.0[a]	-5.5[b]	-7.2[c]
6	-1.7[a]	-5.4[b]	-7.4[c]
7	-1.6[a]	-5.5[b]	-7.1[b]
8	-1.4[a]	-5.4[b]	-7.0[b]
9	-1.4[a]	-5.2[b]	-7.2[c]
10	-1.4[a]	-5.1[b]	-7.0[c]
11	-1.7[a]	-4.9[b]	-6.5[b]
12	-1.8[a]	-4.8[b]	-6.1[b]

* Mean weight loss was adjusted for center and interaction effects.
Values with different superscripts are significant at $p<0.05$.

The unbalanced analysis produced results that were similar to the completers analysis; in general, the p values were lower for the comparisons between the 10 and 15 mg groups. The balanced and carryforward approaches differed from the completers analysis in that the absolute values for weight loss were lower for each group at each month and the values were statistically significantly different for the 10 vs 15 mg groups at all 12 months. At 12 months, the 10 mg group lost approximately 3.0 kg more weight compared to the placebo group and the 15 mg group lost approximately 4.3 kg more weight compared to the placebo group. Peak weight loss occurred at approximately the 6th and 7th months and then declined toward the 12th month.

Figure 8.3.4.2.1 illustrates the adjusted mean percentage weight loss from baseline at each month during the study for the completers.

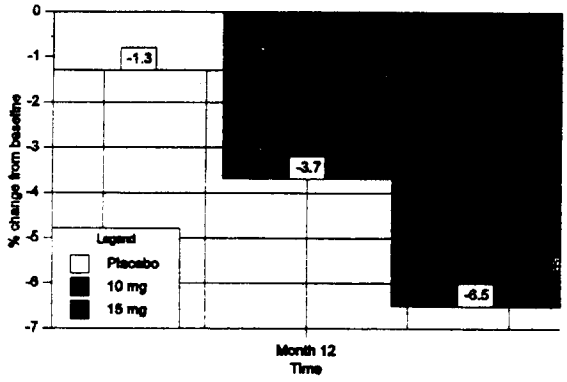
Figure 8.3.4.2.1



Compared to the placebo group, the 10 and 15 mg sibutramine groups lost significantly more weight at each time point ($p<0.001$). Compared to the 10 mg group, the 15 mg group lost significantly more weight during months 2-10 ($p<0.05$). The 10 and 15 mg groups did not differ significantly at months 11 and 12. At month 12, only the 15 mg dose produced a mean percentage weight loss that was at least 5% greater than placebo.

Figure 8.3.4.2.2 illustrates the adjusted mean percentage weight loss from baseline at month 12 for the intent-to-treat - LOCF dataset.

Figure 8.3.4.2.2



At month 12, both the 10 mg and 15 mg groups had a statistically significantly greater percentage weight loss compared to placebo ($p<0.001$). In addition, the 15 mg dose was statistically different from the 10 mg dose ($p<0.001$). It is noteworthy that only the 15 mg dose produced a weight loss that was at least 5% greater than placebo by the end of the trial.

Table 8.3.4.2.3 provides the percentage of patients who lost > 5% of baseline body weight at months 6 and 12 for the completers.

TABLE 8.3.4.2.3

Treatment	Month 6			Month 12		
	n	%	odds ratio	n	%	odds ratio
Placebo	106	26		76	29	
10 mg	116	57●●	3.59	80	56●	2.54

TABLE 8.3.4.2.3						
Treatment	**Month 6**			**Month 12**		
	n	%	odds ratio	n	%	odds ratio
15 mg	124	69●●	6.77	93	65●●	5.40

Odds ratio of success/failure relative to placebo
●p<0.01, ●● p<0.001 compared to placebo

In the intent-to-treat analysis, 20% of placebo subjects, 37% of 10 mg subjects, and 54% of 15 mg patients achieved a weight loss of at least 5% of initial body weight (10 and 15 mg vs placebo, p<0.01).

In an analysis that included weight change from baseline to month 12 including patients who withdrew but returned for the month-12 assessment, the adjusted mean weight losses for the placebo, 10 mg, and 15 mg groups were 1.9 kg (n=98), 4.0 kg (n=99), and 4.9 kg (n=108), respectively. The differences between all pairs of treatment groups were significant at p<0.05.

Waist circumference

The adjusted mean reductions in waist circumference from baseline to endpoint were -3.12 cm, -7.12 cm, and -8.40 cm for the placebo, 10mg, and 15mg groups, respectively. The reductions in waist circumference in the 10 and 15 mg groups were statistically significantly greater compared to placebo (p<0.01).

Consummatory behavior

Subjects who received 10 mg of sibutramine reported reduced hunger and cravings for sweet foods and increased satiety compared to placebo subjects. Subjects who received 15 mg of sibutramine had reduced hunger, appetite, craving for sweet and carbohydrate foods and greater dietary compliance compared to placebo subjects. These findings support the notion that sibutramine works by reducing appetite and cravings for simple and complex carbohydrates.

Patients in the 15 mg group had statistically significantly reduced appetite (p<0.001) and greater dietary compliance (p<0.05) compared to those in the sibutramine 10 mg group.

SAFETY OUTCOMES

8.3.4.3 Adverse events

Table 8.3.4.3.1 provides the number of subjects who withdrew from the study and the reasons for withdrawal.

TABLE 8.3.4.3.1			
REASON FOR WITHDRAWAL	**TREATMENT GROUP**		
	N=163	**N=161**	**N=161**
	Placebo	10 mg	15 mg
Adverse event	24	18	20
Lack of efficacy	10	5	2
Did not attend	31	40	27
Lost to follow-up	-	1	2
Recovered	1	-	1
Protocol violation	6	7	8
Withdrew consent	9	4	2
Domestic situation	1	1	1
Moved from area	-	3	3
Trying pregnancy	1	-	1

There were no statistically significant differences between the groups for overall withdrawal rates. Six subjects in the placebo group, 7 in the 10 mg group, and 8 in the 15 mg group did not provide a post-baseline assessment of body weight. These 21 subjects are not included in the endpoint analyses.

A total of 256 subjects completed the 12 month study. A total of 249 patients were included in the analyses of completers because 7 patients had their 12-month assessments 14 days after the final dose.

Table 8.3.4.3.2 provides the percentages of patients reporting adverse events by COSTART body system.

TABLE 8.3.4.3.2			
BODY SYSTEM	**PLACEBO**	**10 MG**	**15 MG**
	N=163	N=161	N=161
Overall	67%[a]	76%[ab]	82%[b]
Body as a whole	40%	43%	47
Cardiovascular	4%	6%	10%
Digestive	17%[a]	26%[ab]	30%[b]

TABLE 8.3.4.3.2			
BODY SYSTEM	**PLACEBO**	**10 MG**	**15 MG**
Heme and lymphatic	0%[a]	1%[ab]	3%[b]
Metabolic	4%	2%	4%
Musculo-skeletal	9%	12%	14%
Nervous system	15%[a]	24%[ab]	35%[b]
Respiratory	22%	24%	22%
Skin	12%	12%	19%
Special senses	1%[a]	12%[b]	11%[b]
Urogenital	10%	16%	19%

Values with different superscripts are significant at $p<0.001$ except haemic and lymphatic which is significant at $p<0.05$.

Adverse events which appear to have occurred more frequently in the active treatment groups were: pain: back pain, abdominal pain; constipation, nausea, tenosynovitis, dizziness, dry mouth, and pharyngitis.

Table 8.3.4.3.3 provides the adverse events reported by more than 5% of patients.

Table 8.3.4.3.3			
COSTART term	**Placebo**	**10 mg**	**15 mg**
Headache	13	17	11
Infection	18	19	23
Inury/accident	10	9	13
Pain/back	7	10	11
Constipation	5	12	14
Arthralgia	9	7	10
Dry mouth	2	19●	21●
Pharyngitis	13	22	26
Rhinitis	13	5	7

● $p<0.001$ compared to placebo

The Sponsor states that during the one-month follow-up period 30 adverse events were reported by the placebo group, 24 events were reported by the 10 mg group, and 40 events were reported by subjects in the 15 mg group. In addition, five subjects reported depression during the month

of follow-up; two in the placebo group and three in the 15 mg group. There was no evidence of withdrawal according to the Sponsor. However, the depression and anxiety inventories were administered one week following the 12-month endpoint. This may not be an optimal time to administer these inventories as potential withdrawal symptoms may manifest later than one week following the discontinuation of drug therapy.

Table 8.3.4.3.5 provides the details of the adverse events reported as **serious** in the active drug treatment groups.

TABLE 8.3.4.3.4

number	sex	age (yrs)	dose (mg)	duration (days)	event	comment
11	F	49	10	126	4 drop attacks	Hx of epilepsy withdrew
109	F	62	10	22	perforated diverticulum	withdrew
121	F	32	15	246	PVCs	amiodarone prescribed withdrew
424	F	22	15	203	pregnancy	no complications withdrew
3	M	20	10	35	amputation of finger	withdrew
32	F	43	10	130	hysterectomy	reason not provided
34	F	50	10	53	abdominal pain	patient recovered without dx
75	F	53	10	76	vaginal bleed	normal findings at surgery
119	M	61	10	312	urinary fequency	prostatectomy finding unknown
343	F	62	10	85	arthralgia	steriod injection
438	F	47	10	100	abdominal pain	adhesions removed persistant pain withdrew
453	F	48	10	188	urethroplasty	withdrew because of nausea
502	F	37	10	307	colpo-suspension	no reason or findings provided
35	F	48	15	18	irritable bowel syndrome	
53	F	38	15	9	neck pain following an accident	
79	M	61	15	239	chalazia of eyelid	removed surgically
95	F	34	15	222	elective lumpectomy	finding not reported
202	F	34	15	187	surgery for adhesions	recovered
219	F	43	15	258	work-up for arthritis	no definitive dx

TABLE 8.3.4.3.4						
number	**sex**	**age (yrs)**	**dose (mg)**	**duration (days)**	**event**	**comment**
298	M	60	15	129	atrial fibrillation	condition may have predated sibutramine tx ?
369	F	38	15	78	reversal of tubal ligation	
434	M	63	15	364	developed distal neuropathy	
459	F	44	15	247	syncope possible SAH	persistent neurological sxs
464	F	32	15	365	pregnancy	neonatal seizures

Table 8.3.4.3.6 shows the **10 mg** sibutramine subjects who **withdrew** from the study for "non-serious" adverse events.

TABLE 8.3.4.3.5					
number	**sex**	**age (yrs)**	**duration (days)**	**event**	**comment**
75	F	53	245	constipation	resolved
91	F	41	93	carpal tunnel syndrome	outcome unknown
126	M	37	194	chest pains and hypertension	outcome unknown
180	F	52	24	nausea	resolved
182	F	42	180	fluid retention	resolved
206	F	25	47	emotional lability	resolved
257	F	30	62	dizziness	recovered
332	F	37	54	headaches	recovered
335	F	44	4	dizziness	recovered
363	F	64	187	insomnia	recovered
378	F	43	96	migraines	recovered
406	F	34	188	ankle pain	recovered
445	M	58	33	constipation	recovered
453	F	48	?	nausea	recovered

TABLE 8.3.4.3.5					
number	**sex**	**age (yrs)**	**duration (days)**	**event**	**comment**
471	F	40	220	sinusitis	recovered
520	F	48	226	paraesthesia in legs	continued after withdrawal

Table 8.3.4.3.7 shows the **15 mg** sibutramine subjects who **withdrew** from the study because of a non-serious adverse event.

TABLE 8.3.4.3.6					
number	**sex**	**age (yrs)**	**duration (days)**	**event**	**comment**
40	F	30	51	irritability	recovered
45	F	58	207	abnormal LFTs	recovered after 10 weeks
112	F	55	53	emotional lability	recovered
181	F	38	59	panic attacks	recovered
191	F	37	278	palpitations	recovered
205	F	31	22	depressed	recovered
216	M	47	1	nausea, tremor	recovered
218	F	63	264	dry mouth	recovered
231	F	35	14	headaches	recovered
300	F	60	244	cervical spondylosis	recovered
326	F	26	65	sweating	recovered
331	F	34	26	nausea	recovered
344	F	39	19	insomnia	recovered
351	F	49	25	constipation	recovered
478	F	37	248	dizziness	ongoing ?
485	F	36	109	constipation	ongoing at 1-month post-study
499	F	36	8	light headedness	recovered
387	F	21	129	chest pain	ongoing 1-month post-study

Laboratory values

Table 8.3.4.3.4 provides the laboratory values that changed during the trial.

TABLE 8.3.4.3.7					
Variable	**Tx group**	**6 months**	**12 months**	**Endpoint**	**Final**
Platelets (×10⁹/l)	placebo	-	-12.2a n=66	-6.9a n=111	-6.5a n=135
	10 mg	-	8.4b n=74	9.2b n=118	5.9b n=130
	15 mg	-	3.7b n=83	2.3a n=122	3.3b n=134
Triglyceride (mmol/l)	placebo	-0.07a	-	-	-
	10 mg	-0.37b	-	-	-
	15 mg	-0.41b	-	-	-
Eosinophils (×10⁹/l)	placebo	-	-	-	-0.006a n=135
	10 mg	-	-	-	0.024b n=130
	15 mg	-	-	-	0.005a n=134
Creatinine (umol/l)	placebo	-	-3.5ab n=68	-4.0ab n=114	-4.0ab n=137
	10 mg	-	-2.8b n=75	-2.8b n=122	-2.6b n=135
	15 mg	-	-5.9a n=84	-6.2a n=123	-5.9a n=134
Uric acid (umol/l)	placebo	-6.9a n=113	-	-9.1a n=114	-8.7a n=137
	10 mg	-20.2b n=122	-	-21.0ab n=122	-16.9a n=135
	15 mg	-21.6b n=122	-	-26.5b n=123	-28.6b n=134

Values with different superscripts are statistically significantly different at least $p<0.05$

The changes in clinical chemistries were not clinically significant. It should be noted that thyroid function test were evaluated in only one subject at 6 months, one subject at endpoint, and two subjects at the final assessment.

Lipoprotein lipids

At month 6, triglyceride levels were reduced by 3% in the placebo group, 18% in the sibutramine 10 mg group, and 19% in the sibutramine 15 mg group. The reductions in the active treatment groups were statistically significantly different compared to response in the placebo subjects. However, there were no statistically significant differences in triglyceride levels among the three groups at 12 months or endpoint. Total cholesterol levels did not change significantly in the drug or placebo-treated subjects.

Vital signs

There was a small, but statistically significant increase in diastolic blood pressure in the 10 mg group (1.6 mm Hg) compared to the placebo group (-0.9 mm Hg, $p<0.01$) when averaged over all time points. There was also a significant increase in pulse rate in the 15 mg group (3.5 bpm) compared to the placebc group (0.1 bpm, $p=0.007$).

Table 8.3.4.3.8 provides the percentage of patients in each group that had at least one systolic blood pressure reading > 160 mmHg and at least one diastolic blood pressure reading > 90 mmHg during the trial.

TABLE 8.3.4.3.8			
	Placebo	**10 mg**	**15 mg**
% of patients with at least one SBP > 140	43%	51%	46%
% of patients with at least one DPB > 90	27%	34%	35%
% of patients with at least one SBP > 140 or DBP > 90	45%	55%	50%

SBP = systolic blood pressure and DBP = diastolic blood pressure in mm Hg

Table 8.3.4.3.9 illustrates the Pearson correlation coefficients for the change from baseline in body weight vs the change from baseline in both systolic and diastolic blood pressures in the placebo and sibutramine-treated groups.

TABLE 8.3.4.3.9				
	Sibutramine		**Placebo**	
Month	**Δ in SBP**	**Δ in DBP**	**Δ in SBP**	**Δ DBP**

TABLE 8.3.4.3.9				
	Sibutramine		Placebo	
12	0.07	0.12	0.25●	0.13
Endpoint	0.06	0.09	0.26●	0.14

●$p<0.05$

These data illustrate that there were no significant correlations between the change in body weight and the change in systolic or diastolic blood pressure in the sibutramine-treated subjects, whereas there was a significant correlation between the reduction in body weight and a reduction in systolic blood pressure in the placebo group.

Electrocardiograms

The adjusted mean change in heart rate from baseline to endpoint recorded from ECGs increased in the 15 mg group compared to the placebo group (4.9 vs -0.5 bpm, $p<0.01$). Moreover, the adjusted mean change in ECG heart rate from baseline to month 6 increased by 4.5 bpm and 5.8 bpm in the 10 and 15 mg groups, respectively, whereas the mean pulse rate decreased by 1.3 bpm in the placebo group (these changes were statistically significant at $p<0.01$) The adjusted mean change in PR interval from baseline to 6 months was decreased significantly in the 15 mg group compared to placebo (-5.3 vs 4.3 msec, $p<0.01$) as well as compared to the 10 mg group (-5.3 vs 3.0 msec, $p<0.01$). The adjusted mean change in the QT interval from baseline to 6 months was decreased in the 10 and 15 mg groups compared to the placebo group (-7.3 vs 9.1 msec, $p<0.01$ and -12.5 vs 9.1 msec, $p<0.001$, respectively). At endpoint the only significant difference was between the 15 mg group vs placebo (-7.7 vs 6.9 msec, $p<0.05$). These changes do not appear to be clinically significant.

Psychiatric evaluation

The protocol specified that 100 patients would complete the Beck depression and State anxiety inventories. Only 63 and 67 subjects completed these inventories, respectively. There were no significant differences between the groups for these two inventories when compared from the end of the double-blind treatment period to one week after treatment ended. Importantly, these inventories were not administered at baseline, so conclusions regarding any changes in mood from baseline to study completion cannot be made.

8.3.5. SPONSOR'S CONCLUSIONS

"This study demonstrated that sibutramine was efficacious over a 12-month treatment period with statistically significant reductions in weight compared to placebo, up to and including month 12, in mild to moderately obese patients.

The adverse event profile was generally good and sibutramine was well tolerated. Heart rate increased with sibutramine from baseline to month 6; however, it decreased again from month 6 to month 12."

8.3.6 MEDICAL OFFICER'S SUMMARY AND CONCLUSIONS

The results of the 5% responder analysis (completers and intent-to-treat datasets), support the Sponsor's claim that sibutramine was efficacious when compared to placebo over a 12-month treatment period.

In general, this Reviewer agrees with the Sponsor's comment that the adverse event profile was generally good. The Sponsor's comment that pulse rate increased from baseline to month 6 and decreased from month 6 to month 12 is true, but may reflect the drop-out of subjects with elevated pulse rates from month 6 to month 12. Diastolic blood pressure was also increased in the 10 mg group compared to the placebo group (1.6 vs -0.9 mmHg, $p<0.01$). It is worth emphasizing that, in contrast to the significant correlation between the change in weight with the change in systolic blood pressure observed in the placebo group, sibutramine-induced weight loss was not associated with a reduction in blood pressure. In fact, overall, sibutramine-induced weight loss was associated with an increase in diastolic blood pressure.

NON-PIVOTAL STUDIES

8.4 SB 1042 UK

OBJECTIVE/RATIONALE

8.4.1 The objectives of this study were to assess the weight-reducing effects of 1, 10, and 20 mg once-daily doses of sibutramine and placebo and to evaluate the safety and tolerability of sibutramine in an obese population.

DESIGN

8.4.2 A 12-week multicenter (3 centers with 2 Principal Investigators), double-blind, parallel-group, dose-ranging study. This study employed a one-week washout period prior to the start of the study and a 12-week follow-up period.

PROTOCOL

POPULATION

8.4.3.1 Inclusion criteria:
1. Male or female
2. Age____

3. Obese: BMI

Exclusion criteria:
1. Pregnant or lactating women
2. Seated heart rate over 100 bpm
3. Seated diastolic blood pressure greater than 95 mmHg
4. Patients treated for hypertension
5. Presence of significant medical illness
6. Patients taking any medication that may alter body weight
7. Patients who lost more than 3 kg in the previous 3 months

Subjects were provided with written information on appropriate food selections. In addition, subjects had the option of returning to the center at additional times for dietary counseling.

ENDPOINTS

8.4.3.2 The primary endpoint was the change in body weight. Other assessments included blood pressure, heart rate, dietary compliance, and concomitant therapy changes. These endpoints were measured at weeks -1, baseline, weeks 2, 4, 8, and 12. Optional visits (dietary compliance and counseling) occurred at weeks 1, 3, 5, 7, 9, 10, and 11. Follow-up visits was conducted at weeks 16, 20, and 24. Waist and hip circumferences were measured at weeks 0, 12, and 24. Laboratory assessments were conducted at weeks -1, baseline, weeks 4, 12, and 24. An ECG was obtained at baseline and week 12.

STATISTICAL CONSIDERATIONS

8.4.3.3 The change in absolute body weight was the primary endpoint and was analyzed by repeated measures ANOVA with factors for treatment group, investigator, the investigator-by-treatment group interactions, time, and the time-by-treatment group interaction. These analyses were performed on four datasets:
1. Unbalanced-all available data with no account taken for missing values.
2. Balanced-all available data with the missing data replaced. Predicted values were calculated from a model fitted to all available data.
3. LOCF-this approach violated the 70% rule and was therefore only performed for completers.
4. Completers-patients who completed the 12-week, double-blind treatment phase of the study.
Baseline body weights were not equal in the randomized groups. An analysis using ANCOVA was therefore performed to adjust for the unequal baseline values.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.4.4.1 Two-hundred twenty-five patients entered the study. Nineteen subjects withdrew during

the washout leaving 206 who entered the double-blind phase. One-hundred patients completed the 12-week double-blind treatment phase.

Table 8.4.4.1.1 illustrates the reasons for withdrawal and the numbers of subjects who withdrew from the different groups.

TABLE 8.4.4.1.1				
Reason for withdrawal	**Placebo**	**1mg**	**10mg**	**20mg**
	n=51	n=50	n=56	n=49
Adverse event	5	3	7	5
Lack of efficacy	6	14	7	3
Lost to follow-up	6	1	2	3
Protocol violation	0	2	6	0
Other+	10	11	7	8
Total withdrawn	27 (53%)	31 (62%)	29 (52%)	19 (39%)

+ includes patients who lost interest in the study, domestic stress, lack of transport, went on holiday, trial incompatible with work.

There were no statistically significant differences between groups with respect to reason for withdrawal.

TABLE 8.4.4.1.2						
VARIABLE		**TREATMENT GROUP**				**OVERALL**
		Placebo	**1mg**	**10mg**	**20mg**	
		n=51	n=50	n=56	n=49	n=206
Age (yrs)	mean	38.8	39.4	38.8	38.3	38.8
	range					
Sex	male	4	6	7	5	22
	female	47	44	49	44	184
Race	Cauc	51	50	55	49	205
	Af-Amer	0	0	1	0	1
BMI (kg/m^2)	mean	32.2	32.7	32.8	32.3	32.5
	range					

As shown in table 8.4.4.1.2, the groups were balanced with respect to important baseline demographic characteristics. However, the subjects in the 1 mg group in center 2 and the 20 mg subjects in center 3 were older compared to the other groups. There did not appear to be any significant differences between the groups with respect to concomitant drug usage at baseline or during the study.

Table 8.4.4.1.3 provides the protocol violations by treatment group.

TABLE 8.4.4.1.3

Protocol Violation	Placebo	1mg	10mg	20mg	Overall
	n=51	n=50	n=56	n=49	n=206
Visits >3 days earlier than scheduled	2	1	4	3	10
Visit > number of days for which drug was dispensed	15	10	14	14	53
BMI < 27 kg/m^2	4	0	1	2	7
BMI > 40 kg/m^2	2	2	1	1	6
Lost > 3 kg during washout	2	5	4	6	17
ECG abnormality at baseline	0	2	5	0	7
Mildly depressed	0	0	1	0	1
Taking anti-depressant	0	0	1	1	2
On holiday during trial	9	10	8	17	44
Compliance < 70%	7	8	6	3	24
Compliance > 130%	7	7	8	4	25

Five patients (2 in the 10 mg group, 2 in the 20 mg group, and 1 in the placebo group) started taking laxatives during the study. These subjects remained in the study. It does not appear that there were any imbalances in the distribution of protocol violations and thus they most likely did not affect the study results.

EFFICACY ENDPOINT OUTCOMES

Body weight

8.4.4.2 A comparison of the absolute weight loss (kg) in each group from the balanced analysis is shown in the following table 8.4.4.2.1

TABLE 8.4.4.2.1				
BALANCED ANALYSIS				
Week of study	**Placebo** n=41	**1mg** n=37	**10mg** n=45	**20mg** n=41
2	-1.0	-1.3	-1.8	-2.4
vs placebo		p=ns	p=0.01	p=0.01
vs 1mg			ns	p=0.001
vs 10mg				ns
4	-1.6	-1.6	-3.1	-3.8
vs placebo		p=ns	p=0.01	p=0.01
vs 1mg			p=0.001	p=0.001
vs 10mg				p=0.05
8	-3.0	-2.7	-4.6	-5.8
vs placebo		p=ns	p=0.01	p=0.01
vs 1mg			p=0.001	p=0.001
vs 10mg				p=0.05
12	-3.4	-3.4	-5.9	-7.3
vs placebo		p=ns	p=0.01	p=0.01
vs 1mg			p=0.001	p=0.001
vs 10mg				p=0.05

Table 8.4.4.2.2 illustrates the similar results seen in the completers analysis as with those in the other datasets.

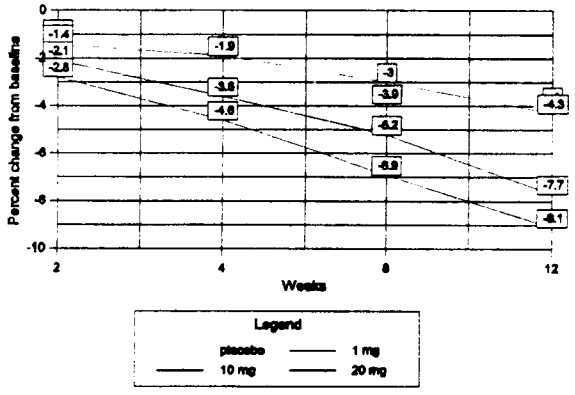
TABLE 8.4.4.2.2				
COMPLETERS ANALYSIS				
Week of study	**placebo** n=24	**1mg** n=18	**10mg** n=27	**20mg** n=30
2	-0.9	-1.5	-2.1	-2.3
vs placebo		p=ns	p=0.01	p=0.01
vs 1mg			p=ns	p=ns
vs 10mg				p=ns
4	-1.7	-2.1	-3.7	-4.0

TABLE 8.4.4.2.1				
COMPLETERS ANALYSIS				
Week of study	**placebo** n=24	**1mg** n=18	**10mg** n=27	**20mg** n=30
vs placebo		p=ns	p=0.01	p=0.01
vs 1mg			p=0.01	p=0.001
vs 10mg				p=ns
8	-3.1	-3.5	-5.8	-6.0
vs placebo		p=ns	p=0.01	p=0.01
vs 1mg			p=0.01	p=0.01
vs 10MG				p=ns
12	-3.5	-4.1	-6.9	-7.6
vs placebo		p=ns	p=0.01	p=0.01
vs 1mg			p=0.05	p=0.01
vs 10mg				p=ns

The results of the analysis of the unbalanced dataset were similar to those of the completers analysis: Ten and 20 mg were statistically superior to placebo and 1 mg at 12 weeks, whereas 10 and 20 mg were not significantly different from one another at week 12.

Figure 8.4.4.2.1 illustrates the percent change from baseline in body weight for the unbalanced dataset.

Figure 8.4.4.2.1



At 12 weeks the placebo, 1 mg, 10 mg, and 20 mg groups had a percentage weight loss of -4.0, -4.3, -7.7, and -9.1%, respectively.

Table 8.4.4.2.3 provides the level of statistical significance for the various differences between

the groups illustrated in figure 8.4.4.2.1.

TABLE 8.4.4.2.3					
Week	**Group**	**N**	**vs placebo**	**vs 10 mg**	**vs 20 mg**
2	placebo	41			
	1 mg	37	ns	ns	0.001
	10 mg	45	0.05		ns
	20 mg	41	0.01		
4	placebo	38			
	1 mg	32	ns	0.001	0.001
	10 mg	44	0.01		0.05
	20 mg	38	0.01		
8	placebo	26			
	1 mg	23	ns	0.05	0.001
	10 mg	30	ns		ns
	20 mg	34	0.01		
12	placebo	24			
	1 mg	18	ns	0.05	0.001
	10 mg	27	0.01		ns
	20 mg	30	0.01		

The results of the balanced and completers datasets were similar to the unbalanced dataset. One exception was the statistically significant difference between the 10 and 20 mg groups at 12 weeks in the balanced dataset.

The results of the analysis of the proportion of subjects losing greater than 5% of baseline weight at week 12 for the completers is shown in table 8.4.4.2.4

TABLE 8.4.4.2.4			
Treatment group	**n**	**Proportion losing > 5%**	**p-value vs placebo**
Placebo	24	42%	
1 mg	18	44%	0.86
10 mg	27	74%	0.02

TABLE 8.4.4.2.4			
Treatment group	**n**	**Proportion losing > 5%**	**p-value vs placebo**
20 mg	30	83%	0.002

Waist circumference

There were no significant differences between the groups with respect to the reduction in waist circumference following weight loss.

SAFETY OUTCOMES

8.4.4.3 A limited number of subjects received extensive exposure to the various drug dosages. Only 16/51, 12/50, 17/56, and 14/49 of the subjects in the placebo, 1mg, 10mg, and 20mg groups, respectively received more than 84 days of exposure.

Adverse events

Seventy-one percent of the subjects in the 20 mg group reported adverse events compared to 43% of the subjects in the placebo group ($p<0.001$) and 44% of the subjects in the 1 mg group ($p=0.01$).

Adverse events reported by more than 5 subjects are summarized in Table 8.4.4.3.1.

TABLE 8.4.4.3.1				
EVENT	**NUMBER OF PATIENTS REPORTING**			
	Placebo	**1 mg**	**10 mg**	**20 mg**
Asthenia	3	1	3	1
Headache	2	2	6	7
React uneval	2	1	2	2
Constip	1	-	5	4
Diarrhea	2	1	2	1
Nausea	1	1	1	4
Thirst	-	-	2	4
Depression	2	1	1	2
Dizziness	-	1	1	6

TABLE 8.4.4.3.1				
EVENT	NUMBER OF PATIENTS REPORTING			
	Placebo	**1 mg**	**10 mg**	**20 mg**
Dry mouth	-	2	2	11
Insomnia	1	1	1	6
Taste perv	-	-	-	7

Details of the adverse events that led to patient withdrawal are summarized in Table 8.4.4.3.2

TABLE 8.4.4.3.2						
Number	**Sex**	**Age**	**Dose**	**Duration**	**Event**	**Comment**
114	F	44	Pl	47	Breast Ca	recovered
162	M	33	20	49	Convulsions	Brain tumor, removed and recovered
199	F	38	20	49	severe constipation	Hemorrhoidectomy
6	F	25	Pl	14	nausea, vomiting	possibly viral
15	F	20	Pl	70	pregnant	terminated
59	F	64	Pl	23	diarrhea	recovered
159	F	38	Pl	21	severe headache	?
78	F	26	1	14	abdominal cramps, diarrhea	?
156	M	33	1	70	hypertension	?
171	F	46	1	7	hypertension	recovered
47	M	37	10	42	renal colic	recovered
154	M	28	10	28	influenza	recovered
160	F	39	10	30	anxious about adverse events	?
172	F	42	10	63	backache	recovered
214	F	29	10	7	hypertension	recovered
217	F	30	10	7	URI sxs	recovered
265	M	46	10	14	abnormal chemistries	normal at 1-month follow-up

TABLE 8.4.4.2						
Number	**Sex**	**Age**	**Dose**	**Duration**	**Event**	**Comment**
74	F	27	20	30	depression, ?hypertension	recovered
97	F	55	20	21	headache, nausea	?
192	F	21	20	63	pregnancy	terminated

Clinical Chemistries

Although there were statistically significant changes in packed cell volume, potassium, and albumin these changes were not clinically significant. In addition, there were no obvious dose-related changes. Urinalysis results did not show any significant changes with drug treatment. There were small and nonsignificant reductions in triglyceride and total cholesterol levels in the 10 and 20 mg groups.

Vital signs

The systolic and diastolic blood pressures decreased slightly at the endpoint assessment. These changes were not statistically significant. Although heart rate measured manually did not change significantly, heart rate measured from ECG did increase significantly in the 10 mg (5.9 bpm) and 20 mg (6.1 bpm) groups ($p<0.01$; 10 and 20 mg vs placebo). The QRS interval decreased in the 10 mg group (-0.9 ms) and in the 20 mg group (-0.2 ms) ($p<0.01$ 10 mg vs placebo and 1 mg; $p<0.05$ 10 mg vs 20 mg)

8.4.5 CONCLUSIONS

Three features of this study merit comment. First, compared to other studies using similar doses, subjects in the placebo group achieved a greater amount of weight loss. Second, this is the only study were the pulse rate (measured manually) was reduced with drug treatment. And third, unlike other studies, blood pressure was reduced with active treatment. However, conclusions regarding the efficacy and safety of sibutramine cannot be accurately made because of the relatively small percentage of subjects who completed the study.

8.5 BP 850

OBJECTIVE/RATIONALE

8.5.1 The primary objective of this 8-week study was to evaluate the weight-reducing effects of 5 and 20 mg QD of sibutramine vs placebo when taken in conjunction with modest caloric restriction, exercise, and behavior modification.

DESIGN

8.5.2 This was a single-center, block-randomized, double-blind, placebo-controlled, parallel-group, 8-week study. The study consisted of a screening visit at week -3, two run-in visits at weeks -2 and -1 and a baseline evaluation at which time qualified subjects were assigned, using a stratified randomization format, to one of two dose regimens of sibutramine (5 or 20 mg) or to placebo. Subjects then entered an 8-week active treatment phase, with evaluations at weeks 2, 4, 6, and 8. A follow-up visit was conducted at week 9. All subjects received an individualized caloric restriction program, an exercise program, and behavior modification. Randomization was performed according to a prospective stratification procedure based upon factors that influence the likelihood of successful weight loss. The likelihood of successful weight loss was computed from points assigned to the following variables: gender, annual family income, habitual nighttime snacking, age of onset of obesity, physician rating of motivation, and weight loss between week -2 and baseline. Four strata were defined. For every six subjects enrolled in each stratum, two were randomly assigned to each treatment group.

PROTOCOL

POPULATION

8.5.3.1 The entry criteria for this study included male or surgically sterilized or postmenopausal women between the ages of _____ . Their body weight had to be between _____ of ideal body weight. Pulse rate and diastolic blood pressure had to be _____ respectively.

ENDPOINTS

8.5.3.2 Standard endpoints included the change from baseline in body weight, blood pressure, pulse, ECG parameters, and laboratory parameters including lipid and thyroid panels.

STATISTICAL CONSIDERATIONS

8.5.3.3 A cursory explanation of the statistical approach was provided in the protocol dated 7/26/89. A detailed description of the statistical techniques was provided in the report section of volume 1.119. The principle efficacy parameter, change in body weight was analyzed in four ways.

1). The observed change in weight from baseline was analyzed using a one-way ANOVA procedure with treatment as the only factor. This was done for each week (2, 4, 6, and 8) separately.

2). An analysis as conducted in 1, except that only those completing the treatment period were included.

3). A repeated measured ANOVA was performed. An incomplete three-way ANOVA with the following factors treatment, subject within treatment, week, and treatment by week.

4). LOCF.
5). Observed change from baseline for weight was analyzed using a two-way ANOVA procedure with treatment, stratum, and the treatment by stratum interaction as factors. This procedure was done for each week separately.
6). The same analysis as that in 5, except that an endpoint analysis was done.
7). A repeated measures ANOVA for overall change in weight was performed; it considered stratification as well as treatment effects. The analyses were performed using an incomplete four-way ANOVA with the following factors: treatment, subject within treatment, stratum, week, and all of the interactions of treatment, stratum, and week.

Categorical assessments of yes or no were made for subject compliance, exercise, and behavior modification. Fisher's exact tests were performed for both the observed and endpoint approaches.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.5.4.1 A total of 331 potential subjects were screened by telephone. Of this number, 126 met the inclusion criteria. One-hundred nine subjects attended the informational meeting, 39 were subsequently excluded. Three subjects decided not to attend the additional screening visits and an additional 7 subjects were excluded during this time. Sixty subjects were thus enrolled in the study: 19 to 5 mg, 21 to 20 mg, and 20 to placebo. Table 8.5.4.1.1 illustrates the mean (range) baseline characteristics of the subjects by treatment group.

TABLE 8.5.4.1.1

	5 mg n=19	**20 mg n=21**	**Placebo n=20**
Age (years)	49.6	46.5	46.5
Sex (% female)	74	66	70
Race (% Caucasian)	94	90	96
Weight (kg)	97.3	101.2	96.0
Height (cm)	168.1	170.0	167.0

There were no statistically significant differences between the groups.

EFFICACY ENDPOINT OUTCOMES

Body weight

8.5.4.2 Table 8.5.4.2.1 provides the percent weight change from baseline for subjects completing the study.

TABLE 8.5.4.2.1					
Visit	**p value**	**Treatment**	**n**	**Mean %**	**Comparison**
Week 2	0.0001	Placebo	19	-0.85	A
		5 mg	18	-1.36	A
		20 mg	18	-2.44	B
Week 4	0.0001	Placebo	19	-1.13	A
		5 mg	18	-2.20	B
		20 mg	18	-4.04	C
Week 6	0.0002	Placebo	19	-1.10	A
		5 mg	18	-2.31	A
		20 mg	18	-4.14	C
Week 8	0.0001	Placebo	19	-1.31	A
		5 mg	18	-2.97	B
		20 mg	18	-5.07	C

Values with different letters are significant at $p < 0.05$.

The results of the other analyses were essentially the same. There were no stratum or treatment by stratum interactions that were significant. In general, the 20 mg dose was statistically and clinically superior to the 5 mg dose as well as to the placebo group at all time points. While the 5 mg group was significantly different from the placebo group at certain time points in some of the analyses, the clinical significance of the differences was minimal.

At week 8 the percent difference in body weights from baseline were -1.27%, -2.78%, and -4.98% for the placebo, 5 mg, and 20 mg groups, respectively.

SAFETY OUTCOMES

Adverse Events

8.5.4.3 There were no serious, unexpected or life-threatening adverse events during the study.

Five subjects withdrew from the study because of an adverse event. One subject in the placebo group experienced a rash. One subject in the 5 mg group complained of headache, dizziness, nausea, cramps, and feeling faint. Three subjects in the 20 mg group withdrew because of adverse events: one because of headache, feeling depressed, fatigued, and early awakening; one because panic attacks, puritis, depression, fatigue, dry mouth, and chills and fever; and one because of stomach pain, heartburn, and decreased appetite.

Symptoms related to the nervous system were reported most frequently. Dry mouth was reported by 32% of subjects in the 5 mg group, 29% of 20 mg subjects, and 20% of placebo subjects. Insomnia was reported by 5% of 5 mg subjects, 33% of 20 mg subjects, and by none of the placebo subjects. Nervousness was reported by 0% of the 5 mg group, 24% of the 20 mg group, and 5% of the placebo group.

Clinical Chemistries

There were no significant changes in serum chemistry values during the study. Similarly, there were no significant changes in thyroid function test values or in urinalysis values.

Lipoprotein Lipids

There were no beneficial changes in serum lipid levels during the study in any of the treatment groups.

Vital Signs

The change in diastolic blood pressure at week 2 was statistically significantly different between the sibutramine and placebo groups (5.26, 4.48, and 0.0 mmHg for the 5 mg, 20 mg, and placebo subjects, respectively, p=0.03). There were no other statistically significant changes in any of the vital sign parameters.

CONCLUSIONS

8.5.5 In this 8-week study of obese patients, 20 mg QD of sibutramine led to statistically significantly greater weight loss compared to 5 mg QD of sibutramine or to placebo. The absolute decrease in body weight in the 20 mg group was approximately 4-5 kg. In general, the drug was well tolerated and there were few drop-outs related to adverse events. There were no significant changes in serum chemistry values, and other than a small increase in diastolic blood pressure in the sibutramine groups, vital signs did not change significantly.

8.6 BPI 851

OBJECTIVE/RATIONALE

8.6.1 To evaluate the weight reducing effectiveness and safety of sibutramine 10 mg QD compared to placebo over a 12 week period in obese subjects. Additional objectives included examining the effects of sibutramine on appetite, food intake, percent body fat, resting metabolic rate, thyroid function, and serum lipid levels.

DESIGN

8.6.2 This was a 12-week, single-center, double-blind, block-randomized, placebo-controlled, pilot efficacy and safety study in 30 obese subjects. There was a 2 week screening period and a post-dosing assessment at 2 to 4 weeks after the completion of the double-blind phase. All patients received counseling by a dietitian and were instructed to consume a diet of 1500 Kcal/day for men or 1200 Kcal/day for women.

PROTOCOL

POPULATION

8.6.3.1 The study population was comprised of male and female subjects aged _____ with a BMI

ENDPOINTS

8.6.3.2 Baseline assessment included body weight, BMI, vital signs, percent body fat, food intake, and resting metabolic rate (RMR). Efficacy (body weight) and safety measurements were performed at weeks 2, 6, 9, and 12. At weeks 2, 6, and 12, an ECG, hemogram, serum chemistry and Modified Norris Assessment evaluations were obtained. Resting metabolic rate was measured at weeks 2 and 12. Percent body fat was assessed at week 12. At weeks 6 and 12 urinalysis, serum lipid, thyroid panel, appetite scale, and food intake determinations were made. Assessment of body composition was done by skinfold thickness, hydrodensitomitry, and total body electrical conductivity. Changes in mental sedation, physical sedation, tranquilization, and other attitudes were assessed using the modified Norris assessment.

STATISTICAL CONSIDERATIONS

8.6.3.3 A two-factor analysis of variance model was conducted to evaluate treatment differences in weight change at weeks 6 and 12. Factors in the model included sex, treatment, and a sex by treatment interaction. Both endpoint (LOCF) and observed analyses were carried out for all efficacy parameters except for the percent of subjects compliant with their diet and changes in percent body fat, where only observed analyses were performed. Endpoint and observed changes from baseline for body weight and BMI were examined using a one-way (by treatment) ANOVA. A repeated measures ANOVA was performed for overall changes in observed body weight and BMI data using an incomplete three-way (by treatment, by subject within treatment, by week, and by treatment by week) ANOVA.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.6.4.1 Thirty-three subjects were screened and randomized to receive placebo (16) or sibutramine (17). Eleven placebo and 16 sibutramine subjects completed the 12 week study.

Table 8.6.4.1.1 provides the baseline demographic characteristics of the study subjects.

TABLE 8.6.4.1.1		
Baseline characteristic	**Sibutramine n=17**	**Placebo n=16**
Age (yrs)	55.8	55
Gender (% female)	82%	94%
Race (% Caucasians)	76%	82%
Weight (kg)	91.9	91.3
BMI (kg/m^2)	34.2	34.3
Skinfold thickness (% bodyfat)	46.8	46.8
Hydrodensitometry (% bodyfat)	49	47.3
Electromagnetic Scan (% bodyfat)	42.4	43.8
Total food intake (g/meal)	470	432
Meal duration (min)	7.9	5.9
Initial rate of intake (g/min)	63.8	75.7
Deceleration of intake (g/min)	2.3	3.0

Values in parentheses are ranges

Four placebo subjects and one sibutramine subject discontinued the study for personal reasons. One additional placebo subject was lost to follow-up.There were a number of protocol violation regarding inclusion and exclusion criteria in both groups. It is unlikely that these violations significantly affected the study results.

EFFICACY ENDPOINT OUTCOMES

8.6.4.2 Table 8.6.4.2.1 provides the mean weight change (kg) from baseline in the observed dataset.

TABLE 8.6.4.2.1				
Visit	**Treatment**	**N**	**Mean**	**P value**
Week-2	Placebo	14	-1.1	
	Sib	17	-2.1	0.08
Week-6	Placebo	11	-2.4	

TABLE 8.6.4.2.1				
Visit	**Treatment**	**N**	**Mean**	**P value**
	Sib	15	-4.0	0.2
Week-9	Placebo	11	-2.4	
	Sib	16	-4.4	0.2
Week-12	Placebo	11	-3.2	
	Sib	16	-5.6	0.2
Week-14	Placebo	11	-3.0	
	Sib	14	-4.7	0.4

The results of the analyses of the endpoint dataset and the repeated measures ANOVA provided similar results; there were no statistically significant differences between the two groups.

Body composition

Changes in body composition were not statistically significantly different between groups. The percent body fat was reduced to a greater extent in the placebo group compared to the sibutramine group when measured by hydrodensitometry (-3.4 vs -2.4%) and electromagnetic scan (-1.3 vs -0.9%). However, these data must be interpreted cautiously as there were different numbers of subjects who had final assessments by the various methods.

Food intake

There were statistically significant reductions in the appetite scale in the sibutramine group compared to the placebo group at week 12 (p=0.001). There were no statistically significant differences between the two groups with respect to the measures of food intake at week 12.

SAFETY OUTCOMES

Adverse events

8.6.4.3 There were no serious adverse events or deaths reported during the study. There were no major differences between the two groups in reported adverse events. Table 8.6.4.3.1 provides the list of treatment-emergent adverse events that occurred in two or more subjects.

TABLE 8.6.4.3.1				
Adverse event	**Placebo**		**Sibutramine**	
	N	# of occurrences	N	# of occurrences
Headache	4	4	5	7
Dry mouth	3	3	2	2
Asthenia	3	6	0	0
Back pain	1	1	2	2
Chest pain	0	0	3	3
Constipation	0	0	3	4
Dizziness	1	1	2	2
Abdominal pain	0	0	2	4
Pain	1	1	1	1
Depression	1	1	1	1
Insomnia	0	0	2	2

Clinical chemistries

There were no significant changes in serum chemistry, thyroid function, or urinalysis values during the study.

Lipoprotein lipids

Total cholesterol decreased by 10.2 mg/dl in the placebo group and by 19.7 mg/dl in the sibutramine group. Triglyceride levels decreased by 60 mg/dl in the placebo group and by 8 mg/dl in the sibutramine group. Similarly, HDL-C levels decreased by 7.0 mg/dl and 4.6 mg/dl in the placebo and sibutramine subjects, respectively. The Sponsor did not provide the results of the statistical analyses for the lipid data.

Vital signs and Electrocardiograms

In general, there were no significant changes in blood pressure during the study in either group. At week 12, the sibutramine group had a statistically significantly higher supine pulse rate (1.3 bpm) compared to the placebo group (-7.5 bpm, p=0.04) When measured by ECG, the heart rate in the sibutramine group was increased by 4.8 bpm at week 12 and reduced by 2.8 bpm in the placebo group (p=0.06). The PR intervals decreased in the sibutramine group and increased in the placebo group, these differences did not reach statistical significance. No other ECG parameters were significantly different between the two groups.

Resting metabolic rate

In the endpoint analysis (LOCF), the resting metabolic rate decreased in the sibutramine group (-106 Kcal/day) and the placebo group (-56 Kcal/day) (p=0.60). In the observed analysis, the RMR decreased by 132 Kcal/day in the placebo group and by 94 Kcal/day in the sibutramine group. These differences are due to the different number of subjects analyzed in the two datasets. The endpoint dataset had 12 placebo subjects and 17 sibutramine subjects, whereas the observed dataset was comprised of 9 placebo subjects and 16 sibutramine subjects.

Mood and affect

In general, the sibutramine group had more favorable changes in the Modified Norris Assessment than the placebo group.

8.6.5 CONCLUSIONS

In this study of obese subjects taking 10 mg QD of sibutramine for 12 weeks, the active drug did not produce significantly more weight loss than placebo (-5.6 vs -3.2 kg, p=0.2). There were no significant changes in percent body fat as assessed by several methods and their were no significant changes in RMR. In general, the drug was well tolerated and did not produce any serious adverse events. Aside from a minor increase in supine pulse rate and heart rate measured by ECG, there were no significant changes in vital signs or ECG parameters.

8.7 SB 1043

OBJECTIVE/RATIONALE

8.7.1 The primary objective of this study was to compare the weight-reducing effects of 5, 10, and 15 mg QD of sibutramine vs placebo in an obese population. An additional objective was to assess the safety and tolerability of various doses of sibutramine.

DESIGN

8.7.2 This study was a multicenter (20), double-blind, placebo-controlled, dose-ranging study. There was a 1-week washout phase followed by a 12-week active-treatment phase and a 4-week post-treatment follow-up period.

PROTOCOL

POPULATION

8.7.3.1 Two-hundred patients were recruited (50 in each group) for this study. Inclusion criteria included:

1. Male or female patients
2. Age
3. BMI

Exclusion criteria included:
1. A seated heart rate of over 100 bpm or a seated diastolic blood pressure greater than 95 mmHg on repeated measurements, or patients being treated for hypertension
2. Patients who lost more than 3 kg in the previous 3 months

ENDPOINTS

8.7.3.2 The primary endpoint in this study was the change in body weight which was measured at screening, baseline, weeks 2, 4, 8, 12, and week 16. Other endpoints included the CGI depression scale, alcohol and tobacco usage, patient assessment of hunger, satiety, and appetite, dietary compliance, waist and hip circumferences, ECG and vital signs, serum chemistries, and adverse event reporting.

STATISTICAL CONSIDERATIONS

8.7.3.3 For the primary efficacy variable: change in body weight, the differences between groups were tested using repeated measures ANOVA with factors for treatment group, center, center-by-treatment group interaction, time, and time-by-treatment group interaction. Williams test was used to make the significance of comparisons among sibutramine groups with placebo and Fisher's LSD method was used to compare mean weight loss between sibutramine groups. Three datasets were analyzed:
1. Unbalanced - all available data with no account taken of missing values.
2. Balanced - missing values will be interpolated
3. All available data using the LOCF.
4. Completers - values from individuals who completed the study.

An intent-to-treat analysis (endpoint) was conducted in which data from individuals who did not have a weight measurement after week 2 were included. The time factor was not included in this ANOVA. The study was powered with 50 subjects in each group to detect a 3.0 kg difference in body weight between the groups.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.7.4.1 Overall, 252 patients were screened for entry into the study between May 13, 1992 and December 7, 1992 at 18 hospital centers. Of these, 16 patients withdrew during the washout, therefore 236 patients entered the double-blind phase of the study. A total of 205 patients completed the 12 week double-blind treatment phase. Two-hundred and twenty-seven subjects

provided an assessment of body weight after week 2 and were included in the primary analysis of weight loss.

There were no statistically significant differences between the treatment groups with respect to drop-out rate. Table 8.7.4.1.1 illustrates the protocol violations for the 4 groups.

TABLE 8.7.4.1.1				
PROTOCOL VIOLATION	**Placebo**	**5mg**	**10mg**	**15mg**
Total number of patients	59	56	59	62
Visit >3 days earlier than scheduled	8	3	7	14
Visit >number of days for which drug dispensed	27	21	28	23
BMI < 27 kg/m2	1	1	0	1
BMI > 40 kg/m2	0	1	1	1
Lost > 3kg during washout	0	1	1	1
Taking prohibited medication	3	8	5	2
Compliance < 70%	7	5	9	

Table 8.7.4.1.2 provides the baseline demographic and physical characteristics of the patients.

TABLE 8.7.4.1.2				
Variable	**Placebo n=59**	**5mg n=56**	**10mg n=59**	**15mg n=62**
Age (yrs)	39.6	39.7	34.8	35.4
# Female	52	52	50	52
# Caucasian	56	54	57	61
Weight (kg)+	84	83.3	85	88.3
BMI (kg/m^2)	32.1	32.4	31.9	33.2

+ median values

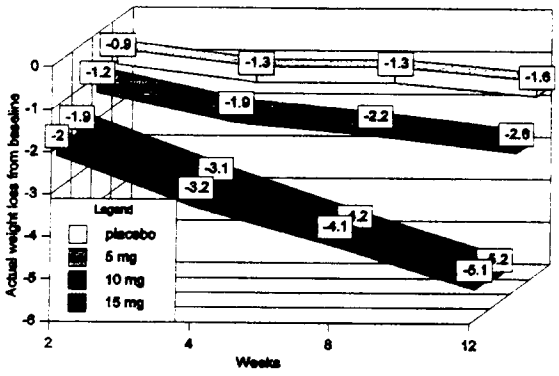
As noted in the above table, the subjects in the 15 mg group tended to be heavier; however, baseline BMIs were comparable across groups. Forty-three patients (18%) had borderline depression, with no treatment group differences. During the study, new concomitant medications were started by 47% of the patients. These included some medications that were prohibited by the protocol: 15 patients took antidepressants/tranquillizers and 5 took laxatives.

EFFICACY ENDPOINT OUTCOMES

Body weight

8.7.4.2 There were significant center effects in all of the datasets analyzed; however, there were no significant center-by-treatment group interactions. The results of the analyses of all the datasets were similar. Figure 8.7.4.2.1 illustrates the adjusted mean change in weight (kg) for the unbalanced dataset.

Figure 8.7.4.2.1



Weight loss in the 5 mg group did not differ from the placebo group. Both the 10 and 15 mg groups lost significantly more weight than the placebo and 5 mg groups ($p=0.01$). There were no statistically significant differences in weight loss between the 10 and 15 mg groups.

The results of the analyses of percentage weight loss were similar to the results of the absolute weigh loss in kilograms. At week 12 the placebo and 5 mg groups lost an average of -1.7% and -3.1% of initial body weight, respectively; the 10 and 15 mg groups lost -6.1% and -5.8% of initial body weight, respectively. Again, the placebo and 5 mg groups did not differ. The 10 and 15 mg groups lost a significantly greater percentage of body weight than the placebo or 5 mg groups. There were no differences between the 10 and 15 mg groups.

Fifty-three percent of the 10 mg group and 58% of the 15 mg group lost > 5% of baseline body weight compared to 19% and 23% in the placebo and 5 mg group, respectively ($p<0.001$).

Waist circumference

Although there were no significant changes in the waist to hip ratio for any of the treatment groups, the waist circumferences were reduced by 3.0, 1.8, 5.9, and 5.2 cm in the placebo, 5 mg, 10 mg, and 15 mg groups, respectively. The reductions of 3.0 and 1.8 cm in the placebo and 5 mg groups, respectively, do not agree with the overall reductions in body weight. It would not be expected to loss a greater proportion of waist circumference with a lower degree of weight loss. The accuracy of the waist circumference is therefore questionable.

SAFETY OUTCOMES

Adverse events

8.7.4.2 The 15 mg group had an increased incidence of adverse events reported for the Digestive and Nervous Systems compared to the placebo and 5 mg groups. However, there were no statistically significant differences in the proportions of patients in each treatment group reporting an adverse event. Table 8.7.4.2.1 illustrates the percentage of patients in each group reporting an adverse event by COSTART body system.

TABLE 8.7.4.2.1				
COSTART	**Placebo**	**5 mg**	**10 mg**	**15 mg**
Body as a whole	36	34	34	37
Cardiovascular	17	9	8	18
Digestive	19	27	27	35
Heme and lymph	-	-	-	2
Metabolic	5	9	3	6
Musculo-skeletal	3	2	7	5
Nervous	29	30	37	47
Respiratory	17	14	5	21
Skin	2	4	5	5
Special senses	-	2	7	3
Urogenital	12	4	8	10
Overall	71	66	71	76

There were no statistically significant differences between the groups with respect to the number of patients reporting the adverse events as mild, moderate, severe, or unknown.

Table 8.7.4.2.2 illustrates the number of subjects in each group reporting the common adverse events.

TABLE 8.7.4.2.2				
COSTART term	**Placebo**	**5 mg**	**10 mg**	**15 mg**
Asthenia	3	3	3	5
Flu syndrome	2	3	1	6
Headache	9	5	6	7
Abd pain	1	2	3	5
Constipation	4	7	10	12

TABLE 8.7.4.2.2				
COSTART term	**Placebo**	**5 mg**	**10 mg**	**15 mg**
Nausea	1	3	3	5
Dry mouth	5	6	6	11
Insomnia	5	6	7	17
Nervousness	4	2	4	4
Pharyngitis	6	4	2	5

Table 8.7.4.2.3 provides the reasons for withdrawal from the study.

TABLE 8.7.4.2.3						
Number	**Sex**	**Age**	**Duration (days)**	**Dose mg**	**Event**	**Comment**
86	F	30	42	10	severe pyelonephritis	Hospitalized and recovered
14	F	30	84	15	sudden deafness in right ear	Cochleo-vestibular syndrome
16	F	23	42	Pl	headaches	recovered
116	F	39	56	Pl	hypertension	unknown follow-up
131	F	48	4	Pl	headache	prescribed dihydroergotamine
149	F	30	35	Pl	dysuria	recovered
22	F	56	63	5	moderate irratiblity	?
151	F	48	70	5	recurrent drowsiness	recovered
205	F	39	56	5	moderate depression	recovered after drug withdrawn
119	F	50	63	10	severe depression	?
127	F	32	35	10	moderate depression	recovered 2-weeks after drug stopped
171	M	25	84	10	insomnia and agitation	recovered after drug stopped
232	F	44	14	10	vertigo	recovered after drug stopped
84	M	30	28	15	epigastralgia	recovered after drug stopped
147	F	51	73	15	hypertension and palpitations	recovered after drug stopped
173	F	41	84	15	migraine	recovered after drug stopped

TABLE 8.7.4.2.3						
Number	**Sex**	**Age**	**Duration (days)**	**Dose mg**	**Event**	**Comment**
221	F	57	70	15	nausea, sweating	recovered 8 days after medication stopped

One subject in the 5 mg group experienced depressive symptoms during the follow-up phase. The patient was hospitalized and the episode resolved by the week 16.

Clinical chemistries

The neutrophil count in the 10 and 15 mg groups declined by -0.2 and -0.3 $\times 10^9$/l, respectively compared to an increase of 0.4 $\times 10^9$/l in the placebo group ($p<0.01$). This difference is not clinically significant. One subject in the 10 mg group had an elevated creatine value at week 12 (242 umol/l).

Lipoprotein lipids

There were no statistically significant differences in the reductions in cholesterol levels among the groups.

Vital signs and electrocardiograms

There were no significant changes in blood pressure to endpoint in the 4 groups. Heart rate increased by 4.2 and 3.8 bpm in the 15 and 10 mg groups, respectively compared to a mean decrease of 2.0 bpm in the placebo group and a 1.2 bpm increase in the 5 mg group. The changes in the 10 and 15 mg groups were statistically significant compared to the placebo group ($p=0.001$). The clinical significance of these minor increases in pulse rate is unknown. The increase in pulse rate in the 10 and 15 mg groups (8.2 and 5.2 bpm, respectively) were higher when measured by ECG than by manual measurement. These changes were also statistically significantly different compared to the change in pulse rate in the placebo group (-3.0 bpm, $p<0.001$). The only statistically significant change noted on ECG was an increase in the QT interval in the placebo group (25.2 ms) relative to the change noted in the sibutramine groups (-8.9, 3.0, and 2.0 ms, for the 5, 10, and 15 mg groups, respectively). The changes in the QT interval are not clinically meaningful.

8.7.5 CONCLUSIONS

This study demonstrated that once-daily doses of 10 and 15 mg of sibutramine produce statistically significantly greater weight loss compared to 5 mg QD of sibutramine and placebo. The absolute amount of weight loss in the 10 and 15 mg groups (approx 5-6 kg at week 12) was similar to the amount of weight lost in the pivotal study BPI 852 as well as other studies using

similar doses. There were however, a number of protocol violations and this increases the potential for bias and reduces the vigor with which one can make conclusions about the study results. As with the other clinical studies involving 10 and 15 mg of sibutramine the consistent finding of increases in pulse and blood pressure are expected pharmacodynamic effects of an inhibitor of norepinephrine reuptake.

CO-MORBIDITY STUDIES

NON-INSULIN DEPENDENT DIABETES

8.8 BPI 853

OBJECTIVE/RATIONALE

8.8.1 The primary objective of this study was to evaluate the effects of four days of 30 mg QD of sibutramine on fasting glucose levels, glucose tolerance during an oral glucose tolerance test, and C-peptide production in a population of obese patients with non-insulin dependent diabetes mellitus (NIDDM). The secondary objective was to evaluate the effects of 12 weeks of treatment with 20 mg QD of sibutramine on body weight, parameters of glucose control, as well as safety and tolerability.

DESIGN

8.8.2 This study was a single-site, placebo-controlled, double-blind, parallel-group study. Eighteen subjects were enrolled in the study. The study included a 3-4 day placebo run-in period and a 5-day placebo-controlled, double-blind inpatient phase. During the inpatient period 12 subjects were randomized to 30 mg of sibutramine QD and 6 subjects were given placebo. An outpatient phase of 12 weeks followed the inpatient phase during which time subjects initially treated with 30 mg QD of sibutramine were treated with 20 mg QD and those subjects initially randomized to placebo remained on placebo during the 12-week period. Patients were allowed to reduce the dose to 10 mg if they suffered an adverse event. The study concluded with a 7-day single-blind placebo washout period.

PROTOCOL

POPULATION

8.8.3.1 The population of this study included patients with a history of NIDDM (duration of at least 3 months prior to the start of the study), obese and age ____, years. Subjects with hypertension who were controlled on a singe antihypertensive agent were also allowed to participate in the study. Oral hypoglycemic agents were permissible. Subjects on insulin were excluded. There is no mention of dietary or exercise education or prescription.

ENDPOINTS

8.8.3.2 The principle endpoints are appropriate and clearly defined in the protocol and included the change in metabolic control, vital signs, and clinical chemistries.

STATISTICAL CONSIDERATIONS

8.8.3.3 The original protocol dated 2/15/91 does not provide the details of the planned statistical analyses. The report dated 9/18/93 from the NDA submission does detail the statistical approaches. It is stated that the changes in fasting glucose levels and body weight were analyzed by a one-way ANOVA and paired t-tests for between and within treatment comparisons. If a subject had missing data for a specific time period that individual was excluded form the analysis of interest. The procedure for handling fall-back doses is not discussed.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.8.4.1 Of the 18 subjects enrolled in the study 6/6 subjects randomized to placebo completed the study and 9/12 randomized to drug completed the study.

Table 8.8.4.1.1 illustrates the baseline demographics for the study participants.

TABLE 8.8.4.1.1

	Placebo n=6	**Sibutramine 30-20 mg n=12**
Male	33%	17%
Female	67%	83%
Black	33%	25%
Caucasian	67%	75%
Weight (kg)	95.2	96.4
Age (yrs)	51.4	52.4
Plasma glucose (mg/dl)	190	201
C-peptide (ng/ml)	40	24
$HbA1_c$ (%)	9.0	8.5

• $p<0.05$

The baseline C-peptide levels were significantly lower in the sibutramine group compared to the placebo group. In addition, there was a greater percentage of males in the placebo group

compared to the active-drug group at baseline.

In the 30-20 mg group, at baseline, one patient was taking captopril and two subjects in this group were taking verapamil. Ten subjects were taking oral hypoglycemics; eight at screening and two at week 13. In the placebo group one subject was taking lisinopril, one subject was taking nifedipine, and one subject was taking lovastatin. Four subjects were on oral hypoglycemics; three at screening and one at week 13.

Three subjects in the sibutramine group withdrew from the study: one because of a hospitalization for foot ulcers, one for personal reasons, and one because of a death in the family.

EFFICACY ENDPOINT OUTCOMES

Body weight

8.8.4.2 The changes in body weight (kg) from baseline for the placebo and sibutramine groups are shown in table 8.8.4.2.1

TABLE 8.8.4.2.1

Visit	Placebo	Within group p	Sibutramine	Within group p	Between group p
Day 4	-0.7	ns	-0.9	<0.05	ns
Week 2	0.0	ns	-1.1	<0.05	p<0.05
Week 4	-0.4	ns	-1.8	<0.05	p<0.05
Week 6	0.5	ns	-2.1	<0.05	p<0.05
Week 8	0.1	ns	-2.2	<0.05	p<0.05
Week 12	-0.5	ns	-2.7	<0.05	ns
Endpoint*	-0.5	ns	-2.6	<0.05	ns
Week 13	-0.5	ns	-2.6	<0.05	ns

*Endpoint includes LOCF n=12

Metabolic control

Table 8.8.4.2.2 provides the changes from baseline in fasting glucose concentrations (mg/dl) in the sibutramine and placebo groups.

TABLE 8.8.4.2.2					
Visit	**Placebo**	**Within group p**	**Sibutramine**	**Within group p**	**Between group p**
Day 4	-15.2	ns	-23.5	p<0.05	ns
Week 2	-3.2	ns	-18.5	ns	ns
Week 4	1.7	ns	8.6	ns	ns
Week 8	23.0	ns	5.9	ns	ns
Week 12	22.0	ns	6.8	ns	ns
Endpoint	22.2	ns	9.3	ns	ns

Table 8.8.4.2.3 illustrates the changes from baseline in glucose concentrations during an oral glucose tolerance test in the sibutramine and placebo groups.

TABLE 8.8.4.2.3						
Visit	**Minute**	**Placebo**	**Within group p**	**Sib**	**Within group p**	**Between group p**
Day 4	0	-15.8	p<0.05	-20.6	p<0.05	ns
	30	-5.2	ns	-36.0	p<0.05	p>0.05
	60	-8.2	ns	-39.7	p<0.05	ns
	90	-1.7	ns	-59.3	p<0.05	p<0.05
	120	-13.8	ns	-52.8	p<0.05	p<0.05
	180	-17.5	p>0.05	-26.0	p<0.05	ns
	240	-27.8	p>0.05	0.6	ns	p>0.05
Week 12	0	10.0	ns	8.2	ns	ns
	30	19.2	ns	8.4	ns	ns
	60	25.0	p>0.05	8.0	ns	ns
	90	19.5	ns	-3.2	ns	ns
	120	17.2	ns	-12.1	ns	ns
	180	24.7	p>0.05	-7.8	ns	ns
	240	12.0	ns	5.8	ns	ns
Endpoint	0	10.0	ns	7.8	ns	ns
	30	19.2	ns	2.2	ns	ns

TABLE 8.8.4.2.3						
Visit	**Minute**	**Placebo**	**Within group p**	**Sib**	**Within group p**	**Between group p**
	60	25.0	p>0.05	7.8	ns	ns
	90	19.5	ns	-22.3	ns	ns
	120	17.2	ns	-27.4	ns	ns
	180	24.7	p<0.05	-15.8	ns	ns
	240	12.0	ns	6.8	ns	ns

As the Sponsor offers, the reductions in glucose concentrations during the day 4 oral glucose tolerance tests most likely reflect the inpatient status of the subjects and their adherence to a "control" diet.

Although the short-term, inpatient treatment with 30 mg QD of sibutramine improved glucose concentrations, treatment with 20 mg QD of sibutramine for 12 weeks did not improve fasting or post-load glucose concentrations

There were no significant changes in the 24-hour excretion of C-peptide in the placebo or sibutramine subjects. Similarly, there were no significant changes in $HbA1_c$ levels by the end of the study in either group.

One subject had his dose reduced from 20 mg QD to 10 mg QD after 2 weeks of treatment because of complaints of constipation, decreased blood pressure, increased pulse, and decreased erectile function.

SAFETY OUTCOMES

Adverse events

8.8.4.4 There were no deaths in this study and no subject withdrew from the trial because of an adverse event. All the patients in the sibutramine group and 83% of the placebo subjects reported at least one adverse event during the trial.

The common adverse events (%) reported during the study are shown in table 8.8.4.4.1

TABLE 8.8.4.4.1		
Event	**Placebo**	**Sibutramine**
Headache	33%	50%

TABLE 8.8.4.4.1		
Event	**Placebo**	**Sibutramine**
Nausea	17%	33%
Pharyngitis	33%	25%
Rhinitis	33%	0%
Pain	17%	25%
Constipation	0%	25%

Vital signs

There were no consistent changes in the supine or standing systolic and diastolic blood pressures in either group. However, one subject (#2, sibutramine) had a transient fall in pre-dose standing systolic blood pressure

In general, there was a minor increase in pulse rate in the sibutramine group compared to the placebo group. Only one subject (#16 sibutramine) had a treatment emergent abnormal pulse value. On day 3 at 7 pm this subjects standing pulse rate was 120 bpm. The change in heart rates calculated from ECGs were similar to those recorded from the radial pulse.

Electrocardiograms

There were no clinically significant changes noted on the ECGs.

Clinical chemistries

The mean platelet count increased by 42 x 10^6/ml in the sibutramine group and decreased by 17 x 10^6/ml in the placebo group. There were no significant changes in serum chemistries with the exception of glucose levels which were described in the efficacy section. There were no significant changes in thyroid profiles.

Lipoprotein lipids

The levels of total cholesterol, LDL-C, and HDL-C decreased from baseline in the placebo group while triglyceride levels increased modestly in this group. In the sibutramine group, levels of total cholesterol, LDL-C, triglyceride, and HDL-C all increased modestly.

8.8.5 CONCLUSIONS

This small study of obese subjects with NIDDM controlled with diet or oral hypoglycemic

agents indicated that the short-term (4-days) administration of 30 mg QD of sibutramine did not adversely affect glucose control and was not associated with significant adverse events. Additionally, 12 weeks of 20 mg QD of sibutramine was generally well tolerated. Glucose control did not change in the sibutramine group despite an average weight loss of 2.7 kg.

In comparison to the studies of patients with uncomplicated obesity, the diabetic subjects in this study lost significantly less weight. There are a number of possible explanations for this finding. First, there were no dietary instructions given to the subjects in this study. The lack of compliance with a reduced calorie diet may reduce the efficacy of the drug. Second, there was a greater percentage of African-Americans in this study; ethnicity may affect the efficacy of the drug. Third, compliance with the study drug may have been low. And finally, it is possible that sibutramine is less effective in patients with type II diabetes mellitus. Further study in a larger population of NIDDM patients is clearly warranted.

8.9 SB 3051

OBJECTIVE/RATIONALE

8.9.1 The objective of this study was to evaluate the effects of 15 mg QD of sibutramine on body weight and glucose control in obese patients with NIDDM.

DESIGN

8.9.2 This was a 2 center, randomized, double-blind, placebo-controlled 12-week study.

PROTOCOL

POPULATION

8.9.3.1 Eligible patients included subjects of either sex, aged ___ years, obese with a BMI greater than ___ and diagnosed with NIDDM of at least six months duration. All patients had a fasting glucose level from three previous visits of ___. Patients with diastolic blood pressures greater than 100 mmHg were excluded; however, patients on stabilized hypertensive therapy were allowed to participate in the study. Stable therapy with sulfonlyureas, metformin, and insulin were acceptable. As part of the study, all patients were seen by a dietitian and provided with a weight-reducing diet.

ENDPOINTS

8.9.3.2 The primary endpoint of this study was the change in body weight from baseline. Secondary endpoints included changes in fasting blood glucose, insulin, and $HbA1_c$ levels; changes in dosage of antidiabetic medications; changes in the area under the curve (AUC) for

glucose and insulin concentrations following a test meal; and the changes in waist and hip circumferences. The change from baseline to endpoint in soft-tissue mass, lean-tissue mass, and fat mass were also calculated. Safety parameters: vital signs, serum chemistries, and reported adverse events were analyzed at several time points during the trial. Several dietary intake and compliance scales were also administered.

STATISTICAL CONSIDERATIONS

8.9.3.3 Differences between the treatment groups in absolute weight loss were analyzed using repeated measures ANOVA, with factors for treatment group, center, the treatment group-by-center interaction, time, and the treatment group-by-time interaction. Four datasets were analyzed:

1. Unbalanced - all available data with no account taken of missing values.
2. Balanced - all available data, but for the within group tests, the missing values were replaced by predicted values calculated from the model fitted to the data. The between group tests including that for treatment were not affected.
3. LOCF - all available data, but with missing values replaced by LOCF for both between and within group tests.
4. Completers - patients who completed the double-blind phase of the study. Missing values were interpolated to ensure complete patient profiles.

Correlation plots of changes in body weight against changes in laboratory variables were also produced. The proportions of patients losing greater than 5% of baseline body weight was calculated with the 95% confidence intervals. The proportion of patients who recorded a change in dosage of diabetic control medication was calculated and the difference between the two groups tested by the Chi-square test statistic.

RESULTS

POPULATION ENROLLED/ANALYZED

8.9.4.1 One-hundred subjects were entered into the study. Nine patients withdrew before the baseline visit, thus 91 patients entered the double-blind phase. Of these, 83 completed the double-blind phase. Seventy-four of these patients continued into the open-labelled study of which the results are published elsewhere (SB 3068). Forty-four patients were randomized to placebo and 47 were randomized to sibutramine. The majority of the patients were enrolled in center 1. Table 8.9.4.1.1 illustrates the baseline characteristics of the two groups.

TABLE 8.9.4.1.1

	Sibutramine n=47	**Placebo n=44**
Age (yrs)	53.7	54.1

	Sibutramine n=47	Placebo n=44
Gender	51% female	55% female
Race	83% Caucasian	75% Caucasian
Weight(kg)*	84.6	82.5
BMI (kg/m^2)	30.6	31.0
Fasting glucose (mmol/l)	10.6	9.8
Fasting insulin (mU/l)	19.9	24.6
$HbA1_c$	9.5	9.4

* median value; values in parentheses represent ranges

The baseline characteristics of the two groups were similar.

Nine subjects in the sibutramine group were controlled with diet alone, while 4 subjects in the placebo group were diet-controlled diabetics. Thirteen subjects in the sibutramine group were taking metformin and 16 in the placebo group were taking metformin. Similarly, 12 subjects in both groups were taking at least one form of insulin therapy. Eleven subjects in the sibutramine group and 1 subject in the placebo group took an antibiotic or other antibacterial agent during the double-blind study period. Seven subjects in the sibutramine group started on a laxative during the study, whereas 1 subject in the placebo group started taking a laxative during this time period.

A summary of the protocol violations are shown in table 8.9.4.1.

TABLE 8.9.4.1.2

Protocol violation	Sibutramine n=47	Placebo n=44
< 11 days between visits	2	2
> 17 days between visits	16	7
BMI < 26.0 kg/m2	1	0
BMI > 35.0 kg/m2	3	3
Fasting glucose < 7 mmol/L	4	4
Fasting glucose > 12.0 mmol/L	13	17
Prohibited med at entry	4	7
Started prohibited med●	9	1
Compliance < 70%	1	1

TABLE 8.9.4.1.2		
Protocol violation	**Sibutramine n=47**	**Placebo n=44**
Compliance > 130%	1	0

✪ Two subjects in the sibutramine group started diuretics, and 7 patients in the sibutramine group and 1 in the placebo group started laxatives.

Two subjects in the placebo group withdrew from the study because of adverse events and 3 withdrew for this reason in the sibutramine group. One subject in each group withdrew consent, and 1 placebo subject was lost to follow-up. The overall withdrawal rate was 9% for both groups.

EFFICACY ENDPOINT OUTCOMES

Body weight

8.9.4.2 Eighty-three subjects completed the study and were included in the completers analysis.

The analyses preformed on all four datasets for the actual weight change from baseline provided similar results. Table 8.9.4.2.1 provides the actual weight change (kg) from baseline for the unbalanced dataset.

TABLE 8.9.4.2.1						
Assessment	**Treatment**	**N**	**Baseline mean**	**Adj mean change●**	**95% CI**	**P value✪**
Week 2	Sib	39	84.9	-0.6	-0.9,-0.3	0.002
	Pl	35	85.8	0.1	-0.2,0.3	
Week 4	Sib	44	86.0	-1.3	-1.7,-0.9	<0.001
	Pl	41	85.6	-0.1	-0.4,0.3	
Week 6	Sib	36	85.9	-1.1	-1.7,-0.7	<0.001
	Pl	32	85.7	0.2	-0.3,0.6	
Week 8	Sib	41	86.0	-1.9	-2.5,-1.3	<0.001
	Pl	36	83.8	0.3	-0.2,0.7	
Week 10	Sib	32	87.2	-1.5	-2.3,-0.8	<0.001
	Pl	33	86.7	0.5	-0.1,1.0	
Week 12	Sib	46	84.9	-2.3	-3.0,-1.7	<0.001

TABLE 8.9.4.2.1						
Assessment	**Treatment**	**N**	**Baseline mean**	**Adj mean change***	**95% CI**	**P value◇**
	Pl	40	85.3	-0.2	-0.7,0.3	

* Adjusted for center and interaction effects and back-transformed from log-transformed data

◇ p-value from the analysis of variance for the difference between the treatment groups in the change from baseline

Using the balanced dataset, the mean percentage change in body weight from baseline to week 12 was -2.8% and -0.3% for the sibutramine and placebo groups, respectively.

Nineteen percent of the sibutramine patients lost > 5% of baseline weight at endpoint and week 12. None of the placebo patients achieved this level of weight loss. The difference between the two groups was not statistically significant.

Body composition

There were no significant changes from baseline to week 12 in the wasit to hip ratios in either group. The mean waist circumference decreased by 1.87 cm in the sibutramine group and by 1.33 cm in the placebo group.

Results of the analysis of change in body composition measured by DEXA are presented in table 8.9.4.2.3

TABLE 8.9.4.2.3				
Assessment	**Placebo**		**Sibutramine 15mg**	
	Baseline mean	Mean change	Baseline mean	Mean change
Whole body	n=38		n=39	
Soft tissue mass (kg)	80.5	-0.5	81.8	-2.6✠
Fat mass (kg)	32.1	-0.2	32.2	-1.8✠
Lean mass (kg)	48.4	-0.3	49.7	-0.8
Percentage fat mass (%)	39.8	-0.1	39.4	-1.0✧
Bone mineral content (g)	2600	-1.5	2755	-13.1

✧ p<0.05 compared to placebo

✠ p<0.001 compared to placebo

Percent fat mass was significantly reduced in the sibutramine group.

Body compositional changes were analyzed for the android and gynoid regions and the changes

were similar to those of the whole body. However, there was a small, but statistically significant reduction in lean mass in the sibutramine group for the gynoid region.
It is of interest to note that the bone mineral content was reduced in the sibutramine group, however, this reduction was not statistically significant.

Metabolic control

There were no significant ($p<0.05$) differences between the two groups with respect to the change from baseline to week 12 in fasting glucose concentrations. The overall changes from baseline in fasting glucose levels were -0.3 mmol/L and 0.9 mmol/L for the sibutramine and placebo groups, respectively.

Similarly, there were no significant differences between the two groups with respect to the change from baseline to week 12 in fasting insulin levels. The overall changes from baseline in fasting insulin levels were 1.7 mmol/L and 1.0 mmol/L in the sibutramine and placebo groups, respectively.

Similarly, there were no significant differences between the two groups with respect to the change from baseline to week 12 or endpoint in $HbA1_c$ levels. Baseline values were approximately 9.4% for both groups and the overall changes from baseline to week 12 were -0.3% and 0.1% for the sibutramine and placebo groups, respectively. The Sponsor reports that there was a subgroup of 15 sibutramine-treated subjects who had a reduction in $HbA1_c$ levels of > 1.0% at endpoint. These 15 subjects also tended to lose more weight than the other active-treated subjects. While the changes in $HbA1_c$ concentrations reported for these 15 patients were favorable, they represent a post hoc-defined subgroup and therefore, reliable conclusions cannot be made regarding their response. Nevertheless, these subjects and their metabolic profiles are discussed further in the results section of SB 3068, the open-label extension phase of this study.

The changes from baseline to endpoint in glucose levels during the test meal are shown in table 8.9.4.2.4

TABLE 8.9.4.2.4

Treatment group	n	Change in kinetics from baseline to endpoint of glucose for patients with complete test meal data		
		C_{max} (mmol/l)	AUC (mmol.min/l)	T_{max} (min)
Placebo	39	0.5	21.0	0.0
Sibutramine	41	-1.1*	-39.0	0.0

* p=0.04 compared to placebo

C_{max}=maximal concentration; AUC=area under the curve; T_{max}=time to maximal concentration

There were no significant differences between the two groups in the changes in AUC or T_{max}

following treatment.

There were no significant differences in the changes in the insulin parameters (C_{max}, AUC, and T_{max}) measured during the test meal in the sibutramine group compared to the placebo group.

Change in antidiabetic medication

Table 8.9.4.2.2 illustrates the changes in antidiabetic medications during the study. There were no statistically significant differences between treatment groups in the proportion of patients who changed their anti-diabetic therapy during the study.

TABLE 8.9.4.2.2

Therapy	Reduction in dose		Increase in dose○		No change in dose●	
	Sib	Pl	Sib	Pl	Sib	Pl
Insulin	2	3	1	2	7	7
Sulfonyl	0	2	2	1	24	21
Metformin	0	0	0	0	13	16
Total	2	5	3	3	42	36

○ One subject started glibencamide (moved from dietary control only)

● Includes five sibutramine patients and two placebo patients who had changes in dose during the study but reverted to original dose by end of the study

Consummatory behavior

There were no significant differences between groups with respect to macronutrient intake, or visual analogue scales for hunger, satiety, or appetite.

SAFETY OUTCOMES

Adverse events

8.9.4.3 The percent of patients in each group reporting an adverse event are provided in table 8.9.4.3.1

TABLE 8.9.4.3.1

COSTART body system	Sibutramine	Placebo
Body as a whole	66	70
Cardiovascular	17	9